Long Term Treatment of Graves’ Hyperthyroidism with Sodium Ipodate*

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ABSTRACT. To investigate the long term usefulness of sodium ipodate (Oragrafin) in the management of Graves’ hyperthyroidism, we studied the effects of ipodate (500 mg, orally, daily for 23–31 weeks) on serum T3, T4, and rT3 concentrations in five newly diagnosed Graves’ hyperthyroid patients. Mean pretreatment serum T3, T4, and rT3 concentrations were 780 ng/dl, 25.4 µg/dl, and 118 ng/dl, respectively. One day after the first dose of ipodate, serum T3 decreased by 62% (P < 0.01), and it was within the normal range thereafter throughout treatment. The serum T4 concentration decreased by 20% (P = 0.09) at 24 h and by 43% (P < 0.05) at 14 days. Subsequently, serum T3 was 41–65% lower than before treatment throughout the study; rT3 increased 24 h after the first dose of ipodate (118% above baseline; P = 0.1), remained elevated (97–109%) for 10 weeks, and then gradually decreased to the pretreatment level. A marked gain in body weight [5.1 ± 1.1 (±SEM) kg] occurred in all patients. After discontinuation of ipodate, mean thyroid radioiodine (RAI) uptake values increased serially in four patients and were similar to pretreatment values: pretreatment, 74 ± 6% (±SEM); after 7 days, 66 ± 8%; after 14 days, 71 ± 7%; after 28 days, 69 ± 7%. The fifth patient’s RAI uptake was 12–16% (vs. a pretreatment value of 48%) from 7–28 days after the end of a 31-week course of ipodate. He remained euthyroid without further treatment for the subsequent 4 months.

We conclude that 1) ipodate (500 mg daily) reduces serum T3 and T4 levels as fast and as much as does the 1-g daily dose studied previously; 2) long term use (for 23–31 weeks) of ipodate for the treatment of Graves’ hyperthyroidism is clinically feasible; no adverse effects occurred during or after ipodate treatment; and 3) RAI uptake returns to pretreatment levels as early as 7 days after the discontinuation of ipodate. Hence, use of ipodate does not prevent use of 131I therapy for those patients for whom it is otherwise desirable. (J Clin Endocrinol Metab 61: 723, 1985)

Subjects and Methods

Patients and studies with ipodate

Five patients with newly diagnosed hyperthyroidism due to Graves’ disease (four men and one woman, ranging in age from 21–55 yr) were studied. The protocol had been approved by the hospital (TSGH) Clinical Research Committee, and written informed consent was given by all patients after they had been informed of the nature and risks of the study. The daily iodine intake in the area in which the patients lived approximated 100 µg (4). The diagnosis of hyperthyroid Graves’ disease was based on clinical examination demonstrating diffuse goiter, elevated serum T3 and T4 concentrations, and increased 24-h thyroid radioiodine (RAI) uptake. The patients were hospitalized for 2 weeks at the beginning and for 4 weeks after the completion of ipodate treatment and were followed weekly during the study in the out-patient clinic. All patients were given 500 mg sodium ipodate (E. R. Squibb and Sons, Inc., Princeton, NJ), orally, as a single dose daily for 23–31 weeks (two patients were treated for 31 weeks, and one patient each was treated for 23, 25, and 28 weeks, respectively). The patients received no other medication during these studies. One to three blood samples were obtained in the 24-h period before ipodate

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administration, and one blood sample was obtained on days 1, 3, and 7 of treatment and then once weekly throughout the study. Body weight and resting pulse were measured before each blood sample was taken. All patients also were questioned about symptoms of hyperthyroidism, including palpitation, nervousness, weakness, and heat intolerance during each visit. They also were questioned frequently for other symptoms, such as nausea, vomiting, and skin rash, that could be side effects of ipodate.

Laboratory studies

Serum T₃, T₄, and rT₃ concentrations were measured by RIAs described previously (5-7). The normal range (mean ± 2 SD) for T₃ was 126 ± 66 ng/dl; for T₄, 8.4 ± 4 µg/dl; and for rT₃, 41 ± 20 ng/dl. All samples from each individual patient were stored frozen and assayed at the same time. Complete blood count, electrolytes, and hepatic and renal function parameters were evaluated before and periodically during treatment. Thyroid ¹³¹I uptake (normal range, 8-30%) was measured in all patients before ipodate administration and 7, 14, and 28 days after the end of treatment. Serum total and inorganic iodine were determined by BioScience Laboratory (Van Nuys, CA) using methods described previously (8, 9). The changes in values at various times of study were examined statistically by analysis of variance (10). The P value is based on Bonferroni t test.

Results

Table 1 shows the serum T₃, T₄, and rT₃ results from each patient before and during the 23- to 31-week treatment period. The mean ± SEM pretreatment serum T₃ level was 780 ± 229 ng/dl; it was 209 ng/dl at 24 h and 170 ng/dl on day 3. These changes represented 62% (P < 0.01) and 69% (P < 0.01) decreases, respectively, in serum T₃ from the pretreatment value (Fig. 1). Mean serum T₃ levels subsequently stayed within the normal range throughout treatment. Patient 2 had a borderline elevated serum T₃ concentration between 24-31 weeks of treatment even though serum T₄ concentrations were normal, and patient 4 had persistently elevated serum T₃ concentrations, although they were 77-83% below the baseline value.

The mean ± SEM baseline serum T₄ level was 25.4 ± 2.6 µg/dl. It decreased by 20% (P = 0.09) at 24 h and by 43% (P < 0.05) at 14 days (Fig. 1). Subsequently, serum T₄ was 41-65% lower than before treatment throughout the study. It was within the normal range in four patients after 10 weeks of treatment. Serum T₄ in the fifth (i.e. no. 4) patient remained supranormal throughout the study, but was 31-56% below the pretreatment value of 35 µg/dl (Table 1). Serum rT₃ increased 24 h after the first dose of ipodate [118% above the mean pretreatment value (118 ± 25 ng/dl); P = 0.1], remained somewhat elevated (78-109%) for the 10 weeks of treatment, and then decreased gradually to the pretreatment level (Fig. 1). Serum TSH was not abnormally elevated in patients while they were taking ipodate (Table 1).

The data on 24-h thyroid RAI uptake before and after ipodate treatment are shown in Table 2. After the discontinuation of ipodate, mean RAI uptake in four patients was similar to uptake before treatment. It was 66 ± 8% 7 days after ipodate, 71 ± 7% 14 days after ipodate, and 69 ± 7% 28 days after discontinuation of ipodate compared to 74 ± 6% before treatment. The fifth (no. 5) patient’s RAI uptake was 12-16% (vs. a pretreatment value of 48%) 7-28 days after the end of a 31-week course of ipodate. He remained euthyroid without further treatment for the subsequent 4 months and then was treated with low doses of methimazole (5-10 mg, daily) and propranolol (20 mg, three times a day) when his serum T₃ and T₄ levels were 140 ng/dl and 10.5 µg/dl, respectively. Patient 5 was clearly euthyroid clinically and chemically. Patient 1 had a slight increase in serum T₄ and a large increase in serum T₃, from 130 to 210 ng/dl. Patients 2 and 4 were clearly hyperthyroid 1 week after stopping ipodate. In the subsequent 3 weeks, serum T₄ remained elevated in patients 1, 2, 4, and 5 1 week after discontinuation of ipodate (Table 2). Patient 5 was clearly euthyroid clinically and chemically. Patient 1 had a slight increase in serum T₄ and a larger increase in serum T₃ from 130 to 210 ng/dl. Patients 2 and 4 were clearly hyperthyroid 1 week after stopping ipodate. In the subsequent 3 weeks, serum T₄ remained elevated in patients 1, 2, 4, and 5, but at no time during the first 28 days after discontinuation of ipodate did serum T₃ or T₄ exceed pretreatment values. During the last weeks of ipodate treatment, serum total and inorganic iodine content were 1082 ± 114 and 110 ± 43 µg/dl, respectively, in four patients. Unfortunately, single samples from only two patients were available for serum iodine determinations in the postipodate period, and each sample was a pool of serum obtained from 7-21 days after treatment. Inorganic iodine levels in these samples were 10 and 12 µg/dl, suggesting rapid clearance of free iodine and the absence of residual ipodate stores available for deiodination.

The changes in body weight and resting pulse rate during ipodate therapy are shown in Fig. 2. The increase in body weight gain was significant after 10 weeks (3.3 ± 0.6 kg; P < 0.01 vs. baseline). The total gain in body weight averaged 5.1 kg after 23 weeks of treatment. The resting pulse rate decreased gradually to 87% of the pretreatment mean value of 90 ± 5 (±SEM) beats/min (P = 0.25) after 20 weeks of ipodate treatment.

Improvement in subjective symptoms of hyperthyroidism, including perspiration, nervousness, palpitation, tremor, and weakness, was reported by all patients. No abnormal results were found on periodic blood tests for complete blood count, electrolytes, and hepatic and renal function during and after ipodate treatment. Chest ra-
TABLE 1. Effect of long term treatment of Graves’ hyperthyroidism with ipodate (500 mg, orally, daily)

Table: Patient no. | Serum conc. of T₄ (μg/dl) | Pretreatment | Day | After ipodate treatment
--- | --- | --- | --- | ---
1 | 27 | 17 | 16.5 | 12 | 14.5 | 13.5 | 7.5 | 6.8 | 8.5
T₃ (μg/dl) | 340 | 200 | 155 | 105 | 110 | 175 | 170 | 210 | 155 | 130
rT₃ (μg/dl) | 58 | 160 | 270 | 205 | 190 | 205 | 220 | 130 | 130 | 110
TSH (mU/ml) | <2.5 | | | | | | | | | |
Mean ± SEM | 25.4 ± 3.1 | 20.0 ± 3.4 | 15.2 ± 1.7 | 14.0 ± 1.0* | 13.2 ± 1.6* | 14.0 ± 1.4* | 9.4 ± 2.9* | 9.8 ± 2.8* | 7.5 ± 0.8* |

*P < 0.05 vs. baseline values [the P value is based on Bonferroni t test for multiple comparisons (10)].

Patient no. | Serum conc. of T₄ (μg/dl) | Pretreatment | Day | After ipodate treatment
--- | --- | --- | --- | ---
2 | 23 | 23 | 23 | 13 | 19 | 17 | 11.5 | 6.0 | 7.2 | 9.2
T₃ | 875 | 240 | 140 | 140 | 160 | 205 | 205 | 110 | 160 | 235
rT₃ | 84 | 175 | 170 | 170 | 190 | 240 | 160 | 97 | 89 | 98
TSH | <2.5 | | | | | | | | | |
Mean ± SEM | 22.5 ± 3.2 | 21.0 ± 4.2 | 18.5 ± 3.7 | 15.0 ± 1.8* | 14.0 ± 1.4* | 14.0 ± 1.2* | 9.4 ± 2.9* | 9.8 ± 2.8* | 7.5 ± 0.8* |

*P < 0.01 vs. baseline values.

Diagrams were normal in all patients before and after the study.

**Discussion**

Recent studies suggest that ipodate is as good as or better than propylthiouracil in controlling hyperthyroidism during the first 3 weeks of treatment (3). The effect of ipodate may be related to its ability to reduce peripheral as well as thyroidal T₄ to T₃ conversion (11-13), curtail the tissue effect of thyroid hormones (14-16), and inhibit the release of thyroid hormones, possibly a result of iodide liberated during the metabolism of ipodate in vivo. The present study demonstrates that ipodate (500 mg, orally, daily) was just as fast and effective in reducing serum T₃ and T₄ in Graves’ hyperthyroid patients as treatment with 1 g daily reported previously (3). The slopes of decline in serum T₃ and T₄ after ipodate treatment were virtually identical in these two studies. The peak increases in serum rT₃ at 72 h were 144 ± 84% and 276 ± 65% in the current 500 mg study and the previous 1 g ipodate study, respectively (not statistically significant).

The present study provides data on long term use of ipodate. Serum T₄ was within normal range in four of the five patients after 10 weeks of treatment. The mean T₃ level stayed within the normal range after day 3 of treatment, although it was slightly elevated in some patients. Using 1.5 g tyropanoate (Bilopaque) daily, Noguchi et al. (17) reported a similar (63%) reduction of T₃ after 1 week treatment in seven hyperthyroid patients; serum T₃ remained decreased at the same level without escape throughout the study period of 10-16 weeks. Serum T₄, on the other hand, decreased in only two patients and was unchanged or increased in the other...
patients with Graves' disease. We specifically excluded patients with toxic nodular goiter from this study because they are prone to Jod-Basedow and are less sensitive to the antithyroid effect of iodine (18). However, we do not know the relative importance of free iodine released from ipodate metabolism in vivo and the various other above-mentioned antithyroid effects of ipodate to the overall beneficial effects of ipodate therapy in hyperthyroidism. A systematic future study of the usefulness (or lack thereof) of ipodate treatment in hyperthyroidism due to causes other than Graves' disease should be interesting.

One obvious criticism of using iodine-containing agents for treating hyperthyroidism has been concern that large increases in serum inorganic iodine (63% of ipodate by weight is iodine) derived from ipodate metabolism that would make a subsequent treatment with radioiodine ($^{131}$I) impossible for a prolonged period. However, the data of our study suggest that this concern may not be well founded; the RAI uptake of our patients returned to pretreatment levels as early as 7 days after the discontinuation of ipodate treatment. This early return of high thyroid RAI uptake appears to coincide with rapid clearance of inorganic iodine from blood after the discontinuation of ipodate treatment. These data suggest that it should be feasible to administer $^{131}$I within a week after withdrawal of 500 mg/day ipodate. They also indicate that remission of Graves' disease had not occurred.

It was intriguing to find increased thyroid uptake values in the postipodate period at a time when the serum inorganic iodine level was still elevated (10–12 μg/dl vs. normal, 0.5–1.0 μg/dl). Addition of stable iodide to the dose of radioiodine has been shown in previous studies to markedly reduce the uptake of radioiodine. This effect of stable iodine is more pronounced in hyperthyroid patients with Graves' disease than in euthyroid patients (19, 20). Thus, thyroid $^{131}$I uptake is inhibited
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at a serum iodide level below 5 μg/dl in hyperthyroid patients, whereas this effect in euthyroid patients requires iodide levels greater than 10–12 μg/dl. However, the situation in these acute studies with stable iodide may not apply to our patients, who had received sodium ipodate for many weeks. The thyroid iodine concentration mechanism may have been altered during this period, and there may have occurred an escape from the acute inhibitory effects of iodide (21). One patient in the present study, whose RAI uptake after treatment was 12–16% (pretreatment, 48%), remained euthyroid without further treatment for 4 months, but hyperthyroidism later recurred. Whether the several months remission was due to spontaneous fluctuation in the severity of his Graves’ disease or can be attributed to ipodate is not known.

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