The Therapeutic Efficacy of Oral Cholecystographic Agent (Iopanoic Acid) in the Management of Hyperthyroidism

Chandrasekhar Bal and Narendra Nair

Radiation Medicine Centre, (B.A.R.C.), Tata Memorial Centre Annexe, Parel, Bombay, India

Five randomly chosen patients with thyrotoxicosis were administered 1 gm of the oral cholecystographic agent iopanoic acid daily for 21 days. There was a marked fall in T3 levels by 75% of the pretherapy value by 96 hr; values remained normal over the 21-day period. T4 values fell significantly by seven days of therapy, and the decreased values were sustained. FT3 and FT4I also showed corresponding decreases in value. All subjects showed clinical improvement by both subjective and objective criteria. During therapy, escape from the effect of iopanoic acid was not encountered. However, after stopping the drug for 2–4 wk, the patients' iodine-131 uptake become as high as the pretherapy level, enabling them to undergo radioiodine treatment for thyrotoxicosis. The treatment strategy can be aimed at achieving quick euthyroidism and in planning radioiodine treatment as early as possible in high risk patients. This treatment may also be useful in preoperative control of thyrotoxicosis.

J Nucl Med 1990; 31:1180–1182

The management of hyperthyroidism per se is a challenging field. Several modalities of treatment are currently available. However, controversy exists as to the optimum therapy in different types of patients. Long-term medical management with antithyroid drugs takes several days or weeks to bring hormone values to euthyroid level.

Oral cholecystographic contrast media when administered to normal subjects results in a sharp and rapid decrease in the serum T3 concentration with modest increase in serum T4 and reverse T3 (rT3) concentration (*1–5*). In contrast to normal subjects, hyperthyroid patients taking sodium ipodate show marked decrease in serum T3 and moderate decrease in T4 concentrations (*6–8*). The question often asked is: Can these patients receive definitive treatment of radioiodine and if yes, what is the earliest time? We wanted to investigate this point by asking patients to undergo radioiodine uptake after stopping iopanoic acid given for rapid control of thyrotoxicosis.

Received Aug. 9, 1989; revision accepted Jan. 16, 1990

For reprints contact: N. Nair, MD, Radiation Medicine Centre, (B.A.R.C.), Tata Memorial Centre Annexe, Parel, Bombay - 400 012, India.

MATERIALS AND METHODS

The criteria for inclusion in the study included:

1. No form of prior treatment taken for hyperthyroidism.
2. Initial clinical and biochemical profile as well as iodine-131 (^{131}I) uptakes confirmed hyperthyroidism (Table 1).

The nature and risk of the study were explained to all the patients and informed consent was obtained. Five patients were given 1 g each iopanoic acid (Telepaque) orally as a single dose daily for 21 days. Serial blood samples were collected on Day '0' and subsequently on Days 1, 2, 4, 7, 14, and 21. All serum samples were stored at −20°C and assayed together to reduce interassay variability. Standard 24-hr uptake was measured during the 2–4 post-treatment weeks using a thyroid uptake probe. The thyroid gland volume was measured from the ^{131}I scan using the formula described by Goodwin et al. (*9*). On each visit, patients were clinically examined and signs and symptoms were recorded.

Laboratory Studies

Serum T3, T4, and T3 charcoal uptake ratios, and thyroid stimulating hormone (TSH) were measured in duplicate by radioimmunoassay (RIA) and immunoradiometric assay (IRMA) using kits obtained from Isopharm Division, B.A.R.C., Bombay, India. The normal ranges were T3 = 70-200 ng/dl; T4 = 4.2-13.0 μg/dl, T3 charcoal uptake = 85%-113%, and TSH = 0.25-4.3 nu/ml. Free T3 was measured by Sephadex Column method as described by Rajan and Samuel (*10*).

The antithyroglobulin antibodies (ATA) and antimicrosonal antibodies (AMA) were measured using kits obtained from Wellcome Diagnostics, Dartford, England. The free hormone indices were calculated. Statistical analyses of paired data were done using two-tailed Student's t-test.

RESULTS

Serial thyroid hormone profiles of these five patients are shown in Table 2. All values are depicted as mean ± standard error of mean (s.e.m.). Twenty-four hours after the first dose of treatment, T3 levels decreased by 55%, and by 96 hr to 75% of pretherapy values ($p <$

TABLE 1
Pretherapy Clinical and Laboratory Data of Five Hyperthyroid Patients on Iopanoic Acid*

Sr. no.	Sex/ Age	Pulse rate	24-hr RAIU (%)	Thyroid† wt (g)	TA ATA	TA AMA	T3 (ng/dl)	T4 (μg/dl)	FT3 (pg/mL)	FT4I	Goiter grade	Post-treatment ^{131}I uptake at 24 hr (%)‡
1	F/45	90	60	27.5	–	+	>800	>20	>60.0	>36.2	III	60 (2)
2	F/38	116	60	10.3	+	+	328	>20	26.9	32.6	I	57 (2)
3	F/38	120	72	18.1	–	+	406	>20	50.4	23.9	II	74 (4)
4	F/32	88	59	35.2	+	+	226	>20	20.5	38.7	III	56 (4)
5	F/35	124	68	14.0	–	+	447	>20	53.6	32.6	II	73 (4)

* Dose: 1 g administered orally for 21 days.
† Standard paper Scan method was used (*9*). TSH values were below the lower limit of detectability (0.05 μU/ml).
‡ Numbers in parentheses indicate weeks after discontinuing iopanoic acid.

0.05). Throughout the study period, the T3 concentration remained within the laboratory normal range.

During treatment a significant decrease in serum T4 concentration ($p < 0.01$) was observed and the nadir was reached on the 7th day of therapy. Pretherapy free T3, which is an indicator of active circulating hormone, was decreased by 50% on Day 1, and by 48 hr it further declined to 69% of pretreatment level ($p < 0.05$). Free hormone indices followed the pattern of total hormone. The FT3I significantly correlated ($r = 0.9879$) with free T3, measured by Sephadex Column method. Serum TSH concentration was below the limit of detectability (0.05 μU/ml) in all subjects throughout the study period. Radioiodine uptake (RAIU) measurements were not statistically significant, as pretreatment and post-treatment values were 64.0 ± 26% and 63.8 ± 4.0%, respectively. Post-treatment values are included in Table I.

Changes in Clinical Symptoms and Signs of Hyperthyroidism

All subjects reported improvement in clinical symptoms, such as nervousness, palpitation, and tremor. The resting pulse rate dropped from the mean pretreatment value of 108 ± 9 to 82 ± 7 ($p < 0.05$) by 48 hr. Change in pulse pressure and weight gain were not appreciable. No side-effects of Telepaque therapy were observed except in one patient who had 4–5 loose bowel motions per day from the second day of therapy. Her stool examination revealed no pathogenic organism and the diarrhea was controlled with loparamide for 2 days.

TABLE 2
Response of Serum T3, T4, FT3 Concentration and FT4I to Iopanoic Acid in Five Hyperthyroid Patients*

Day	T3 (ng/dl)	T4 (μg/dl)	FT3 (pg/ml)	FT4I
0	441 ± 108	>20†	42.2 ± 8.7	32.8 ± 2.8
1	185 ± 22	15.9 ± 2.4	21.5 ± 6.8	25.0 ± 4.5
2	147 ± 17	14.9 ± 2.1	13.2 ± 3.5	22.5 ± 3.7
4	112 ± 14	14.7 ± 2.0	9.9 ± 3.0	20.3 ± 3.2
7	102 ± 16	11.3 ± 1.0	10.0 ± 2.8	15.6 ± 3.1
14	120 ± 9	12.5 ± 2.0	8.2 ± 2.6	15.6 ± 3.1
21	155 ± 21	12.1 ± 1.4	10.4 ± 2.0	15.0 ± 2.2

* Dose: 1 g administered orally for 21 days. Each value is expressed as mean ± s.e.m.
† All laboratory values were reported as >20 μg/dl; for statistical analysis it was taken as 20 μg/dl.

DISCUSSION

Sodium ipodate acid and iopanoic acid are similar in structure and both of them rapidly reduce the T3 level. They have structural homology with thyroxine and behave as competitive inhibitors of 5′-monodeiodinase, an enzyme responsible for T4 to T3 conversion. This substrate competition is not seen with other contrast agents, though all of them contain 3-6 iodine atoms per molecule. These effects are more likely to be related to the chemical structure rather than their iodine content (*3*). Wu et al. (*8*) have compared sodium ipodate (oragrafin) with propylthiouracil (PTU) and concluded that ipodate may serve as a useful adjunct in the early treatment of hyperthyroidism (*8*). However, Roti et al. have compared the effects of sodium ipodate and solution of saturated potassium iodide (SSKI) in 15 patients with Graves' disease and concluded that though decrease in hormone values was sharp, the rebound phenomenon observed after withdrawal of ipodate was severe as opposed to iodine (*11*). The escape of the thyroid gland to iodine block is well known. Hence, SSKI should have produced more rebound effect than sodium ipodate. We can infer that slow and sustained release of iodine, from contrast agents, has a more stimulatory effect on thyroid gland than high doses from SSKI. Wang et al. have treated 40 patients with Graves' disease with a single agent, iopanoic acid 500 mg daily for 1–12 mo (*12*). Similar long-term follow-up data also has been published by Shen et al. (*13*). Their reports indicated that iopanoic acid is not an effective agent for long-term treatment of Graves' disease. Karpman and his colleagues have recently reported an excellent response to sodium ipodate in neonatal hyperthyroidism (*14*).

A small daily dose is as effective as pulsed high-dose therapy viz. 3 g every third day, as advocated by Wu et al. (*6*). In our series, TSH was never above the detectable limit (0.05 μU/ml); in contrast, Kleinmann et al. (*3*) have reported a rise as early as Day 5 following 3 g iopanoic acid in euthyroid volunteers. Although the number of individuals in both study groups was comparable, their physiologic statuses were quite different. The ultrasensitive pituitary regulatory mechanism may be excessively suppressed in hyperthyroidism, which can explain this discrepancy in the results.

The observation of RAIU following the iopanoic acid is very encouraging and agrees with the published data of Shen et al. for a similar number of patients (*13*). We treated all five patients of this protocol with iodine-131. They are currently under follow-up, and are doing well. Hence, there is no doubt that these patients can be treated with radioiodine after 2–4 wk of withdrawal of iopanoic acid/sodium ipodate.

This study indicates that hyperthyroid patients may be quickly stabilized to a euthyroid state so that a definite modality like radioiodine or surgery can be offered. This may be of particular value, where early and rapid control is required, such as in high risk patients, thyrocardiac disease in the elderly, and preparing for surgery.

REFERENCES

1. Biirgi H, Wimpfheimer C, Berger A, et al. Changes of circulating thyroxine, triiodothyronine and reverse triiodothyronine after radiographic contrast agents. *J Clin Endocrinol Metab* 1976; 43:1203–1210.
2. Suzuki H, Kadena N, Takeuchi K, Nakagawa S. Effects of three-day oral cholecystography on serum iodothyronines and TSH concentrations: comparison of effects among some cholecystographic agents and the effects of iopanoic acid on the pituitary thyroid axis. *Acta Endocrinologica* 1979; 92:477–488.
3. Kleinmann RE, Vagenakis AG, Braverman LE. The effect of iopanoic acid on the regulation of thyrotropin secretion in euthyroid subjects. *J Clin Endocrinol Metab* 1980;51:399–403.
4. Beng CG, Wellby ML, Symons RG, et al. The effect of ipodate on the serum iodothyronine pattern in normal subjects. *Acta Endocrinologica* 1980; 913:175–178.
5. Suzuki H, Noguchi K, Nakahata M, et al. Effect of iopanoic acid on the pituitary-thyroid axis: time sequence of changes in serum iodothyronines, thyrotropin and prolactin concentrations and response to thyroid hormones. *J Clin Endocrinol Metab* 1981; 53:779–783.
6. Wu SY, Chopra IJ, Solomon DH, Benett LR. Changes in circulating iodothyronines in euthyroid and hyperthyroid subjects given ipodate (oragrafin): an agent for oral cholecystography. *J Clin Endocrinol Metab* 1978; 46:691–697.
7. Wu SY, Chopra IJ, Solomon DH, Johnson DE. The effect of repeated administration of ipodate (oragrafin) in hyperthyroidism. *J Clin Endocrinol Metab* 1978; 47:1358–1362.
8. Wu SY, Shyh TP, Chopra IJ, et al. Comparison of sodium ipodate (oragrafin) and propylthiouracil in early treatment of hyperthyroidism. *J Clin Endocrinol Metab* 1982; 54:632–634.
9. Goodwin WE, Cassen B, Bauer FK. Thyroid gland weight determination from thyroid scintigram with postmortem verification. *Radiology* 1953; 61:88–92.
10. Rajan MGR, Samuel AM. Adapting the total T3 RIA kits to measure serum free T3. *Int J Med Res* 1988; 87:179–185.
11. 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* 1985; 22:489–496.
12. Wang YS, Tsou CT, Lin WH, Hershman JM. Long-term treatment of Graves' disease with iopanoic acid (Telepaque). *J Clin Endocrinol Metab* 1987; 65:679–682.
13. Shen DC, Wu SY, Chopra IJ, et al. Long-term treatment of Graves' hyperthyroidism with sodium ipodate. *J Clin Endocrinol Metab* 1985; 61:723–727.
14. Karpman BA, Rapoport B, Filetti S, Fisher DA. Treatment of neonatal hyperthyroidism due to Graves' disease with sodium ipodate. *J Clin Endocrinol Metab* 1987; 64:119–123.