

Rapid Preoperative Preparation for Severe Hyperthyroid Graves' Disease

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Thyroidectomy (TX) is no longer the preferred choice for the therapy of hyperthyroid Graves' disease but is an alternative in patients who are noncompliant with or have reactions to antithyroid drugs, have moderate to severe ophthalmopathy, have large goiters, or who refuse ^{131}I therapy and/or long-term antithyroid drug therapy. Seventeen clinically and biochemically severely thyrotoxic patients (16 female, mean age of 35 yr), all but one with large goiters, underwent TX after rapid preparation. The potent inhibitors of the deiodination of T_4 to T_3 , iopanoic acid (IOP) (500 mg twice a day) and dexamethasone (DEX) (1 mg twice a day), were given with propylthiouracil or methimazole, when possible, and β -blockers. Thyroid function tests were obtained before treatment and at TX.

All patients were thyrotoxic (mean \pm SE: T_4 , 21.6 ± 1.2 $\mu\text{g}/\text{dl}$; free T_4 index (FTI), 10.3 ± 0.8 ; total T_3 , 510 ± 48 ng/dl). IOP and DEX rapidly lowered T_3 values ($P < 0.0001$; total T_3 , 147 ± 13 ng/dl) with a smaller but significant ($P < 0.05$) decrease in T_4/FTI (T_4 , 17.9 ± 1.3 $\mu\text{g}/\text{dl}$; FTI, 7.9 ± 0.6). All patients were clinically euthyroid before surgery. None developed hypoparathyroidism, laryngeal nerve damage, or worsening of ophthalmopathy after surgery. The restoration of hyperthyroid Graves' disease to euthyroidism is rapidly accomplished with IOP and DEX, β -blockers, and, when possible, antithyroid drugs. This is especially relevant in noncompliant patients with large goiters. (*J Clin Endocrinol Metab* 89: 2142–2144, 2004)

SUBTOTAL THYROIDECTOMY (TX) is the oldest form of therapy for hyperthyroid Graves' disease and remained the only therapy for many decades. Surgery has been replaced to a large extent by ^{131}I treatment or antithyroid drug therapy. Although TX is no longer the preferred choice for the therapy of hyperthyroid Graves' disease, it is still an alternative in patients who are noncompliant with or have serious side effects to the antithyroid drugs, have very large goiters, or who refuse ^{131}I therapy (1, 2). Another special circumstance is the presence of moderate to severe ophthalmopathy because worsening of eye disease is more likely to occur after radioiodine than after surgical therapy (3, 4). To perform TX, euthyroidism should be restored to decrease the surgical risk. Conventional preoperative preparation for TX includes antithyroid drugs and iodine administration before surgery and often takes months to render patients euthyroid. Far more rapid control of thyrotoxicosis can be achieved by the oral administration of iodinated radiographic contrast agents (IRCAs) such as iopanoic acid (IOP) or ipodate, often given in combination with corticosteroids and antithyroid drugs, and β -blockers. IRCAs have a multitude of effects on thyroid physiology and thyroid hormone metabolism. They competitively inhibit types 1 and 2 5'-monodeiodinase in the liver, brain, and thyroid, thereby blocking the conversion of T_4 to T_3 . This leads to a rapid and persistent reduction of T_3 , while reverse T_3 levels increase due to decreased clearance of reverse T_3 (5–8). IRCAs also decrease serum T_4 levels in

hyperthyroid patients due to a decrease in the thyroidal organification of iodine and thyroid hormone secretion from the gland due to the iodine released from these agents (9–11). However, serum T_4 levels decrease more slowly with IRCAs than with potassium iodide treatment, probably reflecting the decrease in the plasma clearance rate of T_4 and a decrease in the hepatic uptake of T_4 by displacement of T_4 from hepatic binding sites (12). Iodine released from IRCAs also reduces intraoperative blood loss by decreasing thyroid vascularity (13–15). Corticosteroids also have multiple effects on thyroid physiology. Large doses of dexamethasone (DEX) reduce T_4 -to- T_3 conversion in peripheral tissues due to an inhibitory effect on 5'-monodeiodination (16). They also decrease serum concentrations of T_4 in patients with Graves' disease by reducing T_4 secretion either by a direct thyroidal effect or by lowering the production of thyroid-stimulating Ig (16).

Variable combinations of IRCAs, glucocorticoids, thionamides, and β -blocking drugs have been given in the preoperative preparation of hyperthyroidism due to Graves' disease, diffuse/nodular goiter, or amiodarone-induced thyrotoxicosis (Table 1). The present report describes the use of IOP in combination with DEX and β -blocking drugs, and, when possible, thionamides, in a large number of hyperthyroid patients in whom surgery was indicated.

Patients and Methods

We rapidly prepared 17 clinically and biochemically severely thyrotoxic patients for TX with IOP, DEX, methimazole (MMI) or propylthiouracil (PTU), and β -blockade (see *Rapid preparation protocol*). Twelve patients had hyperthyroid Graves' disease, four had a toxic multinodular goiter, and one had amiodarone-induced thyrotoxicosis (combination of type 1 and type 2). Sixteen patients were women. Mean age was 35 yr.

The indication for surgery was either unsuccessful treatment with antithyroid drug therapy due to noncompliance, moderate to severe

Abbreviations: DEX, Dexamethasone; FTI, free T_4 index; IOP, iopanoic acid; IRCA, iodinated radiographic contrast agent; MMI, methimazole; PTU, propylthiouracil; TX, thyroidectomy.

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TABLE 1. Previous reports on the use of iodinated radiographic contrast agents for preoperative preparation for hyperthyroidism

Ref.	Disease	No. of patients	Agent	Dose (mg)	Days of treatment
19	Graves' disease	7	Iodate ± β -blocker	500 QD	5
21	Diffuse/nodular goiter	14	IOP ± β -blocker, DEX	500 Q6h	5
15	Graves' disease	14	Iodate ± β -blocker ± PTU	500 BID	3
20	AIT ^a	7	MMI + KClO ₄ followed by IOP	1000 QD	7–20

QD, Every day; Q6h, every 6 h.

^a AIT, Amiodarone-induced thyrotoxicosis (AIT I in six patients, AIT II in one patient).

TABLE 2. Thyroid function tests at baseline, 4 d after treatment and before surgery, and after TX (normal values)

	Thyroid function tests (mean ± SE)			
	T ₄ (4.5–10.9 μ g/dl)	FTI (1–4)	Total T ₃ (60–181 ng/dl)	TSH (0.35–5.5 μ U/ml)
Baseline	21.3 ± 1.2	10.2 ± 0.8	500 ± 48	<0.01
Mean d 4 of Rx	18.7 ± 1.2	8.2 ± 0.7	188 ± 23	NM
Before surgery (mean d 7)	17.7 ± 1.3	7.8 ± 0.6	143 ± 13	NM

To convert T₄ values to nmol/liter, multiply by 12.9; total T₃ to nmol/liter, multiply by 0.0154; and TSH to mIU/liter, multiply by 1. NM, Not measured; Rx, treatment.

ophthalmopathy, refusal of ¹³¹I therapy, and/or very large goiters. Fifteen of 17 patients were admitted to Boston Medical Center to assure compliance. Twelve patients were prepared with IOP, DEX, and MMI (30 or 40 mg daily), and two patients were prepared with IOP, DEX, and PTU (150 mg three times a day or 200 mg three times a day). Three patients were treated with IOP and DEX alone because they developed complications to the antithyroid drugs.

All patients underwent subtotal or near-total TX under general anesthesia using standard operative techniques for TX. Thyroid weight and gross pathological and histological analyses were performed on all thyroid specimens. When hypocalcemia occurred, postoperative serum calcium and parathyroid hormone concentrations were measured. Thyroid replacement therapy was initiated once hypothyroidism was documented.

Rapid preparation protocol

All patients were treated with 500 mg IOP twice a day, 1 mg DEX twice a day, and MMI or PTU, if tolerated. β -Blockade was also started or continued in all 17 patients and titrated to heart rate response.

Thyroid function tests (T₄, free T₄ index (FTI), and total T₃) were obtained before treatment, on d 4 of treatment, at the time of TX (on average, 7 d after initiation of the protocol), and, on average, 28 d after TX. Hormone measurements were carried out in the Boston Medical Center Clinical Laboratory by ADVIA Centaur assays (Bayer Corp., Tarrytown, NY) (TSH: two-site sandwich immunoassay using direct chemiluminometric technology; T₄, total T₃, and T₃ resin uptake: competitive immunoassay using direct chemiluminescent technology). FTI was determined by multiplying total T₄ by the T₃ resin uptake and dividing by 100.

Statistical analysis

Data are expressed as mean ± SE. Pre- and postoperative thyroid function tests were compared by the paired Student's *t* test. *P* < 0.05 was considered significant.

Results

Thyroid function tests at baseline, 4 d after treatment was begun and just before surgery, and after TX are shown in Table 2. All patients were biochemically severely thyrotoxic at baseline. The rapid preparation protocol rapidly lowered serum T₃ values in all patients (*P* < 0.0001). The mean total T₃ concentration at the beginning of therapy was 500 ng/dl (7.7 nmol/liter); at the time of TX, mean total T₃ was markedly reduced to 143 ng/dl (2.2 nmol/liter) (Table 2). In the majority of patients (n = 13), total T₃ levels had returned to

the normal range after 4 d of treatment. Only two patients still had slightly elevated serum total T₃ values at the time of surgery. The remaining 15 patients had total T₃ levels well within the normal range. The decrease in serum T₄ and FTI was far less but still statistically significant (*P* < 0.05) (Table 2).

All patients underwent subtotal or near-total TX after a mean of 7 d of treatment. Surgery was uncomplicated in all cases. The postoperative course was also uncomplicated. No patient developed thyroid storm, persistent hypoparathyroidism, vocal cord paralysis, or worsening of ophthalmopathy, as assessed by clinical inspection, symptoms, and by the use of an exophthalmometer. None of the patients had adverse effects from IOP. Mean weight of the gross pathological specimens was 56 g, with a range of 24–162 g. Histopathological evaluation revealed treated Graves' disease in 12 patients and multinodular goiter in five patients. None demonstrated histopathological findings of thyroid malignancy.

Fifteen of the 17 patients followed up at our institution. Eleven patients had serum TSH values less than 0.01 μ U/ml at 7–28 d after TX, and four patients had serum TSH values from 0.10–48 μ U/ml at 18–138 d after surgery. All 15 patients later developed hypothyroidism and began a L-T₄ replacement therapy.

Discussion

Our results demonstrate that preoperative preparation for severe hyperthyroid Graves' disease can be rapidly and easily accomplished by the simultaneous administration of IOP and DEX along with β -blockade and, when possible, thionamide drugs. This pharmacological combination effectively and rapidly restores euthyroidism by four different mechanisms: inhibition of thyroid hormone synthesis (thionamides), inhibition of thyroid hormone secretion (iodine released from IOP and DEX), inhibition of the conversion of T₄ to T₃ (IOP and DEX), and decrease of the peripheral effects of thyroid hormones (β -blocker). After only 4 d of treatment, serum T₃ concentrations markedly decreased, with a far smaller decrease in serum T₄ values. After 7 d of treatment,

15 of the 17 patients were biochemically euthyroid with serum T₃ levels within the normal range. All patients were clinically euthyroid. Overall, serum T₄ levels decreased far less than serum T₃ concentrations, probably due to decreased plasma clearance of T₄ (12).

Comparative studies with saturated solution of potassium iodide *vs.* ipodate in addition to MMI demonstrated that ipodate was more efficacious in reducing serum T₃ levels and heart rate, consistent with its inhibitive effect on 5'-monoiodinase that does not occur with saturated solution of potassium iodide administration (11, 17). Although IRCAs are very effective as short-term treatment, they do not play a significant role in the long-term management of Graves' disease because their prolonged administration may be associated with a high rate of relapse of hyperthyroidism and a poor response to subsequent MMI treatment (18). IRCAs are tolerated extremely well. None of our patients developed any adverse effects. Potential side effects include mild gastrointestinal complaints, dysuria, and (very rarely) acute renal failure, which is only seen with single doses higher than 6 g (7). Surgery was uncomplicated, and all the patients who were seen in follow-up developed hypothyroidism, as expected.

Our results, which showed that euthyroidism can be restored quickly, effectively, and safely, are similar to those obtained in previous reports in which variable combinations of IRCAs, glucocorticoids, thionamides, and β -blockers were used for the preoperative preparation of hyperthyroidism due to Graves' disease, diffuse/nodular goiter, or amiodarone-induced thyrotoxicosis (15, 19–21). The present report is the largest series of patients with severe hyperthyroid Graves' disease successfully prepared for surgery with IOP, DEX, β -blockers, and in most, thionamides. Two of the previous reports on the preoperative preparation of Graves' disease used ipodate, which is no longer available in the United States (15, 19).

In summary, the present study demonstrates that the rapid restoration of thyrotoxic Graves' disease to euthyroidism is easily accomplished by the simultaneous administration of IOP, DEX, a β -blocker and, when possible, PTU or MMI. This procedure is especially relevant in noncompliant patients with large goiters.

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