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Radioiodine treatment of Graves' hyperthyroidism with and without anti-thyroid medication pretreatment in an Australian teaching hospital

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Abstract

Background: Anti-thyroid drugs (ATD) are routinely used in Australian practice as first-line therapy for Graves' hyperthyroidism (GH) prior to ^{131}I (radioiodine) treatment. There is concern that patients who do not receive ATD pre-treatment will develop uncontrolled hyperthyroidism before and after ^{131}I therapy and that ^{131}I therapy without ATD pre-treatment may not be as efficacious as with ATD pre-treatment.

Methods: We reviewed the records of consecutive patients with GH who received ^{131}I over an 18 months period and compared patients who had not received ATD pretreatment with those who had, in respect to outcomes and episodes of uncontrolled hyperthyroidism post treatment. Ninety-three ^{131}I treatments ("episodes") were administered to 82 patients, nine of whom required more than one treatment. Fifty episodes were preceded by pre-treatment ("Group A"), 41 were not ("Group B") and two episodes were associated with unknown pre-treatment status.

Results: There were no significant differences between Groups A and B in respect to; success of treatment, final thyroid status after treatment or episodes of uncontrolled hyperthyroidism Of the 13 patients who required further therapy with either ^{131}I or surgery after their initial ^{131}I episode, there were no differences in terms of pre ^{131}I characteristics or outcomes within this subgroup compared to those who had received ATD prior to ^{131}I and those who had not. None of the ^{131}I episodes led to uncontrolled hyperthyroidism that necessitated hospitalization or the supervised use of ATD following ^{131}I therapy.

Conclusion: The use of ATD prior to ^{131}I therapy did not influence the outcome of ^{131}I therapy in terms of efficacy in this cohort. Neither the incidence nor the time of onset of hypothyroidism following ^{131}I therapy was significantly affected by the use of ATD pretreatment. There were no episodes of uncontrolled hyperthyroidism following ^{131}I treatment. ATD pre-treatment is not a prerequisite for successful ^{131}I therapy.

Keywords: Graves' hyperthyroidism, radioiodine, anti thyroid drugs, Australia

Introduction

Although approx 60-70% of patients with Graves' hyperthyroidism (GH) are not euthyroid 10 yr following treatment with one or other of the anti-thyroid drugs (ATD) namely, Propylthiouracil and Carbimazole [1], these drugs are routinely used in Australian practice as first-line therapy [2]. Radioiodine (^{131}I) is used mainly in older patients and for recurrent disease. In the presence of significant ophthalmopathy, most endocrinologists avoid the use of radioiodine, although this is controversial. Moreover, ATD are associated with significant side effects, including agranulocytosis [1,3] and some authors have suggested that their use may be obsolete [4]. On the other hand, ^{131}I therapy is a safe and effective treatment for GH and, in the US, approx 70% of endocrinologists would choose ^{131}I as first line therapy [1], but in Australia the rate is lower at 20% [2]. There is concern that patients who do not receive ATD pretreatment will develop uncontrolled hyperthyroidism following ^{131}I therapy and that ^{131}I therapy without ATD pre-treatment may not be as efficacious as with ATD pretreatment [5]. Here, we addressed these concerns by comparing two groups of consecutive patients with GH treated with ^{131}I namely, those who received ATD for 12 months before ^{131}I (Group A) and those who did not receive such pre treatment (group B).

Clinical subjects and methods

We reviewed the records of consecutive patients with GH who received ^{131}I therapy between July 2002 and December 2003 at Geelong Hospital, Victoria, Australia. A data-base was constructed and analyzed with respect to patient characteristics, % uptake on a pre-^{131}I pertechnetate nuclear medicine scan, dosage of ^{131}I administered, and outcome including; thyroid function test results at 3, 6, 12 and 24 months following ^{131}I and the prevalence of post ^{131}I uncontrolled hyperthyroidism ("radiation thyrotoxicosis"). The diagnosis of GH was based on typical symptoms and signs of hyperthyroidism, suppressed thyroid stimulating hormone (TSH) level, raised free thyroxin (T4)

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level, typical appearances on pertechnetate thyroid scanning, positive Thyroperoxidase and thyroglobulin antibodies and positive TSH receptor (TSHr) antibodies The ^{131}I dose was chosen on the basis of the size of the gland on ultrasound or, if this was not available, a combination of impressions from clinical and nuclear medicine findings including pertechnetate uptake percentage. In those patients who had taken ATD, the drug was ceased 5-7 days prior to ^{131}I. Patient demographics and radioiodine treatment details are summarized in (**Table 1**). ^{131}I treatment was considered unsuccessful when symptomatic and biochemical hyperthyroidism persisted for 3 or more months following therapy. Uncontrolled (post ^{131}I therapy) hyperthyroidism was defined as significantly symptomatic hyperthyroidism necessitating prompt medical treatment with or without hospitalization, including the introduction or re-commencement of ATD.

Other tests

Plasma free thyroxin (fT4) and TSH and serum thyroglobulin and thyroid peroxidise antibodies were measured by Barratt and Smith Pathology, Sydney, Australia, using commercial kits according to the manufacturers' instructions. TSH-r antibodies were measured as TSH-r binding inhibiting immunoglobulin (TBII) using a commercial kit according to the manufacturer's instructions Local Ethical Committee approval was received for the study and informed consent of participating subjects was obtained.

Results

Ninety-three ^{131}I treatments ("episodes") were administered to 82 patients, nine of whom eventually required further therapy namely; ^{131}I (9 patients) or thyroidectomy (2 patients). The average dose of ^{131}I administered was 12 mill curies (mCi) (444 megabecquerels or MBq). Fifty episodes were preceded by ATD treatment (Group A), 41 were not (Group B), and two had unknown ATD treatment status. In group A patients, ATD had been initiated by primary care physicians, not by an endocrinologist. Outcome data were available for 88 episodes.

There were no significant differences between Groups A and B. in respect to; success of treatment, final thyroid status after treatment (outcome) or episodes of uncontrolled hyperthyroidism (**Table 2**). Thirteen patients whose initial treatment episodes had been unsuccessful, and who required further therapy with either ^{131}I or surgery after their initial ^{131}I episode, were younger and had an average % pertechnetate uptake that was higher compared to the total cohort average (**Table 1**). Overall, this group did not display any differences in respect to i) pre ^{131}I characteristics or ii) outcomes compared to those who had received ATD prior to ^{131}I. None of the ^{131}I episodes led to uncontrolled hyperthyroidism that necessitated hospitalization or the supervised use of ATD following ^{131}I therapy. While there were three episodes of hyperthyroidism following ^{131}I treatment for which the patient took ATD, none of these patients had been advised to do so by the medical teams involved, and in two of these patients the ATD was promptly stopped.

Table 1. Patient demographics and radioiodine treatment details in patients with Graves' hyperthyroidism pre-treated or not with anti thyroid drugs.

Group	Mean age (yr)	Number (Male/Female)	Episodes of ^{131}I treatment	Average ^{131}I Dose ([1]mCi)	^{131}1 pertechnetate Uptake (%)
Total cohort	49	12 (M), 79 (F)	93	12	10
A ([2]ATD)	50	8 (M), 42 (F)	50	11	13
B (no ATD)	46	4 (M), 37 (F)	41	12	9
Unknown treatment status	Not known	0	2	12	10
Unsuccessful	41	3 (M), 11 (F)	14	11	16

[1]mCi=millicuries, [2]ATD=Anti thyroid drugs (Propylthiouracil, Carbimazole).

Table 2. Outcome of radioiodine treatment in patients with Graves' hyperthyroidism pre-treated or not with anti thyroid drugs.

	Hypothyroidism Post ^{131}I				[1]Euthyroid	[2]Unsuccessful	[3]Unknown
Group	3 mo	6 mo	12 mo	24 mo			
Total cohort	50/93 (54%)	6/93 (6%)	5/93 (5%)	2/93 (2%)	**7/93 (8%)**	**18/93 (19%)**	5/93 (6%)
A ([4]ATD)	26/50 (52%)	3/50 (6%)	4/50 (8%)	2/50 (4%)	5/50 (10%)	9/50 (18%)	1/50 (2%)
B (no ATD)	23/41 (56%)	3/41 (7%)	1/41 (2%)	0/41 (0%)	1/41 (2%)	9/41 (22%)	4/41 (10%)
Unknown treatment status	1/2 (50%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	1/2 (50%)	0/2 (50%)	0/2 (50%)

[1]Number of patients who remained euthyroid throughout study period (24 mo),
[2]Unsuccessful=patient remained or became biochemically and clinically hyperthyroid during follow-up,
[3]Unknown=no follow-up, [4]ATD=Anti thyroid drugs (Propylthiouracil, Carbimazole).

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Discussion

The use of ATD treatment in patients with GH is routine in some centers but not proven to be associated with an acceptable long term remission rate compared to ^{131}I given as the initial treatment [1]. In Australia, ATD therapy is generally used, for 12-18 months, as the initial treatment, ^{131}I use being reserved for those patients who relapse after stopping the medication [2]. In other countries, particularly the US, patients are often initially treated with radioactive iodine in Beta blocker without intervention of anti-thyroid medication [1]. They become hypothyroid and are then treated with thyroxin and this is considered to be most cost effective management. In many countries, including Australia, patients are reluctant to be treated with radioactive iodine initially because of fear of radiation and most endocrinologists accept this and do not try to convince their patients otherwise.

However, there may be advantages of using ^{131}I as the initial treatment, including possible harmful effects of ATD when used before ^{131}I [5-8]. For example, Hancock et al., [6] have reported that Propylthiouracil discontinued 4-7 days before radioiodine dosing is associated with a significant increase in the failure rate of a single dose of radioiodine. These authors showed that in patients who require treatment with Propylthiouracil before radioiodine therapy a higher total serum thyroxin level at diagnosis was associated with an increased rate of radioiodine failure; they concluded that consideration should be given to empirically increasing the dose of radioiodine administered to Graves' disease patients who have received Propylthiouracil before radioiodine administration in an effort to decrease the radioiodine failure rate [6]. Here, we have compared two groups of patients who were treated with ^{131}I namely, those who were pretreated with ATD (Group A) and those who were no (Group B) in respect to successful outcome, final thyroid status and side effects, in particular episodes of uncontrolled hyperthyroidism. To summarize the main results, there were no significant differences between Groups A and B in respect to; success of treatment, final thyroid status after treatment or episodes of uncontrolled hyperthyroidism None of the ^{131}I episodes led to uncontrolled hyperthyroidism that necessitated hospitalization or the supervised use of ATD following ^{131}I therapy.

These results do suggest that there is no advantage in pre treating patients with ATD before radioactive iodine unless one could identify, from the severity of the autoimmune reactions, the size of the thyroid from real-time ultrasonography, levels of TSH receptor antibodies, family history, association with eye disease and other manifestations of Graves' disease, those patients who were likely to remain well in the long term once the ATD has been ceased. Of course, this is difficult to achieve as most patients would take their chances with anti-thyroid medication and hope that once stopped they would remain in remission. However, even in the context of the Australian way of managing this disorder, most patients could be strongly recommended initial treatment with radioactive iodine, with Beta blocker as indicated for symptoms, and the rest would be treated with anti-thyroid drugs, particularly as it appears that the prevalence of long term remission in this latter group is more than 50% in the West Sydney area of Australia [Wall, Champion et al., unpublished observations].

The relatively high prevalence of hypothyroidism following ^{131}I therapy (65-70%) in our patients, in comparison with figures from the published literature (up to 30-40% at 2 years and 5% per year thereafter) [3,4], is an unexpected finding because the average doses of ^{131}I used in both groups were within the recognized range of 5-15 millicuries used in GH [1]; possible explanations for this include the larger glands encountered in this cohort or the mild iodine deficiency that exists in this party of Australia [9].

Conclusion

The notion that pre-treatment with anti-thyroid medication for 12 months before radioiodine (in those who relapse) somehow helps the patient to remain euthyroid following cessation of medication is not borne out by this study. Efforts should be made to stratify patients at the first clinic visit to determine who would be likely to relapse after a course of anti thyroid drugs and who would likely remain well long term and to treat the former group with radioactive iodine initially, the so-called US model.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	JRW	DTSM	CBS
Research concept and design	✓	✓	--
Collection and/or assembly of data	--	✓	✓
Data analysis and interpretation	--	✓	✓
Writing the article	✓	✓	--
Critical revision of the article	✓	✓	--
Final approval of article	✓	✓	✓
Statistical analysis	--	✓	--

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