RADIO-IODINE THERAPY OF HYPERTHYROID GRAVES' DISEASE — THE BLOEMFONTEIN EXPERIENCE

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Objectives. The aim of this study was to investigate effectiveness, action rate and eventual complications of radio-active iodine (RAI) therapy in our patients with hyperthyroid Graves' disease.

Design. Retrospective analysis of clinical results.

Setting. Departments of Internal Medicine, Nuclear Medicine and Biostatistics at the University of the Orange Free State, Bloemfontein.

Subjects and outcome measures. Forty-three patients with Graves' disease (38 women and 5 men) aged 19 - 67 years, mean body mass index 25.0 kg/m^2, were treated with 10 - 15 mCi RAI between 1994 and 1997. Response to the therapy was monitored clinically (complications, body mass index) and biochemically (serum free thyroxine (T_4), thyroid stimulating hormone (TSH) levels) at regular intervals. Results recorded at 6, 12, 16 and 52 weeks were statistically evaluated.

Results. All patients had diffuse enlargement of the thyroid gland. Iodine-131 (131-I) uptake was increased (6 hours 67.3%, 24 hours 79.9%). After RAI therapy 35/43 patients (81.4%) were cured with a single dose of RAI (34 patients became hypothyroid, 1 patient remained euthyroid) and 8/43 patients (18.6%) needed a second dose of RAI. Hypothyroidism occurred 6 - 52 weeks after the RAI therapy, in most cases after 3 - 4 months (94% of finally hypothyroid patients). Replacement therapy with Eltroxin was started on average 13 weeks after RIA therapy. Transient central hypothyroidism was present in 15/34 finally hypothyroid patients (44.1%) Graves' ophthalmopathy was clinically diagnosed in 13/43 patients (30.2%) before RAI therapy and worsened in 2/13 patients (4.6%), who required corticosteroid treatment. No other complications of RAI therapy were found. The mean weight gain of patients was 4.0 kg within 3 months after RAI therapy.

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Conclusions. A single dose of 10 - 15 mCi of RAI was effective in 81.6% of patients with Graves' disease. A second dose of RAI should be considered if patients are still hyperthyroid 4 months after RAI therapy. We did not observe any complications of therapy except moderate worsening of ophthalmopathy in 2/13 patients.

S Afr Med J 1999; **89:** 797-801.

Three different forms of treatment are used for Graves' hyperthyroidism, namely antithyroid drugs, surgery, and radioactive iodine (RAI). The treatment policy for Graves' disease varies from country to country, but RAI therapy is increasing in popularity.[1] In the USA the first choice of treatment for uncomplicated Graves' disease in middle-aged women is antithyroid drugs (30%), surgery (1%), and iodine-131 (69%).[2] The corresponding figures in Europe are 77% for antithyroid drugs, 1% for surgery and 22% for RAI.[3] In Japan antithyroid drugs are the first choice in 88% of cases, surgery in 1% and iodine-131 in 11%.[4] The main drawback of antithyroid drug treatment is the high relapse rate, which varies between 20% and 75%.[5-7] Surgery is a feasible therapeutic alternative and can be considered the treatment of choice in patients with a large goitre, especially those with symptoms of compression, and patients who prefer surgical treatment to other alternatives. The risk of relapse of hyperthyroidism has been reported to be 1 - 28% after surgery.[8,9]

The advantage of RAI therapy is its effectiveness, low risk, low cost and the fact that it is easy to perform.[1] It is widely accepted that most patients with Graves' disease will develop hypothyroidism after the treatment and will need thyroxine substitution.[10] The only possible disadvantage of RAI therapy is the increased risk of development or worsening of ophthalmopathy observed by some authors,[11] although other studies have not confirmed this.[5,12]

The aim of this study is to assess the effectiveness, action rate, and eventual complications of RAI therapy in our patients with hyperthyroid Graves' disease.

Subjects and methods

This is a retrospective study of 43 patients (38 women and 5 men) with hyperthyroidism due to Graves' disease who were treated with RAI at our clinic between 1994 and 1997. The mean age of patients was 39.6 years (range 19 - 67 years), and the mean body mass index (BMI) 25.2 kg/m^2 (range 15.0 - 44.9 kg/m^2). The diagnosis of Graves' disease was confirmed by the presence of symptoms and signs of hyperthyroidism, by elevated serum free thyroxine (free T_4) levels and suppressed thyroid stimulating hormone (TSH) (SimulTrac* Free T_4 (57Co)/Thyroid stimulating hormone (125I); ICN Pharmaceuticals, Diagnostic Division) and an increased 24-hour uptake of iodine-131 (131-I) by the thyroid gland. Patients with nodular goitre were excluded from the study on the basis of their technetium scintigraphy. The patients had no history of previous thyroid gland resection and were not treated with carbimazole before or after the RAI therapy.

The levels of free T_4, TSH and 131-I uptake before therapy are shown in Table I. A single oral dose of 10 - 15 mCi 131-I was administered based on thyroid size, 131-I uptake, and the measurement of effective half-life of the isotope in the thyroid.[13] The response to therapy was monitored clinically and biochemically (free T_4, TSH levels) at regular intervals. Results recorded at 6, 12, 16 and 52 weeks were statistically evaluated.

Table I. Laboratory results of patients with Graves' disease (N = 43)

	T_4 (pmol/)	TSH (mU/ml)	131-I uptake (%/6 h)	131-I uptake (%/24 h)
Mean	103.3	0.18	67.5	76.2
SD	40.4	0.02	20.2	15.2

TSH = thyroid stimulating hormone; SD = standard deviation.

The reference ranges are as follows: free T_4: 9 - 21 pmol/l; TSH: 0.4 - 5.0 mU/ml; 131-I uptake: 6 hours: 10 - 45%, 24 hours 10 - 45%.

Statistical analysis

Continuous variables were summarised by means and standard deviations, or percentiles if the data had a skew distribution. Categorical variables were summarised by frequencies and percentages. Inter-group comparisons of continuous variables were done using 95% confidence intervals (CIs) for mean or median differences, and *t*-tests or Mann-Whitney *U*-tests. Within-group comparisons of continuous variables were done using 95% CIs for mean and median changes, and paired *t*-tests or signed rank tests.

Results

After RAI therapy 35/43 patients (81.4%) were cured with a single dose of radio-isotope and 8/43 (18.6%) of patients needed a second dose of RAI (34 patients became hypothyroid, 1 patient remained euthyroid 1 year after therapy). Hypothyroidism occurred 6 - 52 weeks after the RAI, in most cases after 3 - 4 months (Fig. 1). Twenty-five out of 34 (73.5%) of finally hypothyroid patients became hypothyroid 3 months after RAI therapy and 32/34 (94%) by 4 months after therapy. Replacement therapy with Eltroxin (levothyroxine sodium) was started on average 13 weeks after RAI.

Patients treated with single and repeated doses of RAI did not differ significantly in age, BMI, and level of free T_4 before the RAI therapy (Table II). The uptake of radio-iodine by the

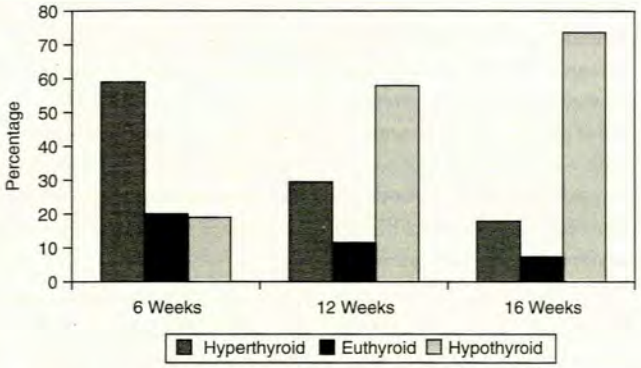

Fig. 1. Outcome of RAI therapy (N = 43).

thyroid gland also did not differ significantly between the two groups (Table II).

Table III shows the levels of free T_4 before and 6 weeks after the RAI therapy. Six weeks after RAI therapy the average levels of free T_4 significantly decreased in comparison with pre-treatment levels ($P < 0.01$). The decrease in free T_4 levels was more pronounced in patients successfully treated with a single dose of RAI (95% CI for difference in median change in single-dose patients versus patients with second dose. Free T_4 levels in patients who needed a second dose of RAI therapy were still high 6 weeks after the first dose and showed only non-significant decline.

Levels of TSH were still suppressed in 37/43 patients (86%) 6 weeks after RAI therapy. TSH levels were suppressed not only in all 26 hyperthyroid patients but also in 8/9 (88.8%) euthyroid and in 6/8 (75%) patients who became hypothyroid 6 weeks after RAI therapy. Twelve weeks after RAI therapy another 17 patients became hypothyroid and 7 of them had inappropriately suppressed TSH levels despite having low free T_4 levels. Sixteen weeks after RAI therapy 2/7 newly hypothyroid patients had suppressed TSH levels. By the time replacement therapy with Eltroxin was started in finally

Table III. Free T_4 levels (pmol/l) before and 6 weeks after RAI therapy

RAI therapy	Total group (N = 43)	Single-dose group (N = 35)	Second-dose group (N = 8)
Before RAI			
Median	118	116	126.5
Range	(23.7; 174)	(36.4; 174)	(23.7; 149)
6 wks after RAI			
Median	35.9	23.6	94.5
Range	(2.3; 174)	(2.3; 140)	(35.9; 174)
P-value	< 0.001	< 0.001	< 0.742
95% CI	36.3; 81.9	44.8; 97.1	–77.8; 150.3

hypothyroid patients, TSH levels were still suppressed in 15/34 (44.1%). Graves' ophthalmopathy was initially present in 13/43 patients (30.2%), and worsened in 2/13 patients (15.3%), who required corticosteroid treatment. No other complications of therapy were reported. The mean weight gain of patients was 4 kg after 3 months and 8.5 kg 12 months after the therapy. Eight patients increased their weight by more than 10 kg 1 year after the therapy.

DISCUSSION

Our data showed that 81.4% of patients with Graves' disease were cured with one dose of radio-iodine. Only 18.6% of patients needed a second dose of RAI. This result is comparable with other published studies that show failure of single-dose cure in 0 - 41% of patients.[1,6,7,14] In our study the failure of a single-dose cure was not related to the pre-treatment levels of free T_4 or the percentage of radio-iodine uptake by the thyroid gland. The success of RAI therapy is influenced by the size of the thyroid gland and possibly by circulating levels of thyroid-stimulating antibodies (TSAb). Responses to RAI therapy are lower in patients with very large glands (> 80 g) and high TSAb levels than in patients with

Table II. Radio-isotope therapy of Graves' disease (N = 43)

Dose	Age (years)	BMI (kg/m²)	Free T_4 (pmol/ml)	131-I uptake (%/6 h)	131-I uptake (% /24 h)
Single (N = 35)					
Mean	39.6	24.6	101.6	66.7	75.1
SD	13.0	5.0	40.39	21.1	15.8
Second (N = 8)					
Mean	39.7	27.7	110.3	71.0	80.7
SD	10.4	8.2	42.8	16.2	11.9
P-value	NS	NS	NS	NS	NS

BMI = body mass index; SD = standard deviation; NS = not significant.

smaller glands.[14] When giving RAI therapy, we use the calculated dose of radio-isotope. We aim at a definitive and early cure from hyperthyroidism to avoid a prolonged thyrotoxic state. Low-dose 131-I therapy has a high rate of single-dose therapeutic failure and was effective in preventing hypothyroidism only over the short term.[15,16] A cure rate of 100% has been reported using as high an absorbed dose as 300 Gy, but this procedure should be restricted to selected patients.[17] Opinion about the timing of the second dose of radio-iodine differs among centres. The second dose of radio-iodine was recommended for patients with hyperthyroidism persistent beyond 2 months of therapy.[18] In other centres a second dose of radio-iodine is not given until 6 months after therapy.[19] The majority of patients who were cured with one dose of RAI developed hypothyroidism within 3 - 4 months after therapy (94% by 4 months). These patients also had a significant decrease in free T_4 levels as early as 6 weeks after the therapeutic dose of isotope, while the patients who needed more than one dose to be cured showed almost no decrease in T_4 levels 6 weeks after RAI treatment. For this reason we suggest that a second dose of RAI should be considered in patients who are still hyperthyroid 4 months after therapy, especially in those with no or minimal decrease in free T_4 levels 6 weeks after RAI therapy.

Serum levels of TSH were still suppressed in 15/34 hypothyroid patients at the time that replacement therapy with Eltroxin was started. This means that 44% of finally hypothyroid patients experienced a transient central hypothyroid phase. This central hypothyroid phase is defined as the presence of suppressed or inappropriately normal TSH levels despite low free T_4 levels following RAI therapy.[20] There is probably a delay in activation of the hypothalamic-pituitary-thyroid axis. For that reason the decision about the initiation of replacement therapy cannot be based on measurement of TSH levels only. Ophthalmopathy is present in about one-third of patients with Graves' disease.[21] A similar percentage (30.2%) of patients were found to have exophthalmos in our study. Only two patients experienced worsening of exophthalmos during the months following RAI therapy.

Controversy remains surrounding the effect of radio-iodine on Graves' eye disease.[22] The recent study by Bartalena *et al.*[23] provides conclusive evidence that radio-iodine treatment of Graves' hyperthyroidism carries a small definitive risk of the development or worsening of ophthalmopathy. It has been proposed that a greater risk for the development of ophthalmopathy is associated with rapid decrease in thyroid function due to destruction of thyroid tissue by the isotope and expression of thyroid antigens.[11] Prolonged hypothyroidism following RAI therapy and smoking are known to be independent risk factors for ophthalmopathy.[12,24] Other authors have found that the common denominator for the development of ophthalmopathy was more severe and unstable disease.[5] In our study the number of patients with worsening exophthalmos was too small for statistical evaluation. Both patients had high levels of free T_4 before RAI therapy and one of them needed a second dose of isotope to be cured, but the same conditions were present in some other patients without ocular problems. They were non-smokers. Because of frequent clinic visits none of our patients experienced prolonged periods of hypothyroidism. In both patients exophthalmos improved after oral corticosteroid therapy. We did not treat other patients prophylactically with steroids.

Recently, a randomised study of 450 patients has confirmed that glucocorticoids (0.4 - 0.5/kg of prednisone) begun 2 - 3 days after radio-iodine treatment, continued for 1 month and then tailed off over 2 months, improved existing ophthalmopathy in the majority of patients and appeared to completely prevent the development of new eye disease.[23] The administration of prednisone to all patients with Graves' disease after radio-iodine treatment will probably not be acceptable clinical praxis. The percentage of patients with worsened ophthalmopathy is low and changes are very often mild and transient.[25] In patients with more severe ophthalmopathy and especially those with active eye disease, it seems prudent to treat hyperthyroidism with an antithyroid drug or to administer prednisone if radio-iodine is given.[25]

Weight gain is a common problem in cured hyperthyroid patients.[1] Our patients gained on average 4 kg within 3 months after RAI therapy and most of them were still regaining their premorbid weight. A weight gain of more than 10 kg was recorded in 8 patients 1 year after therapy. Weight gain beyond the estimated original weight was reported in patients treated for Graves' disease with RAI as well as surgery.[26]

In conclusion, a single dose of 10 - 15 mCi of RAI was effective in 81.6% of patients with Graves' disease. A second dose of RAI should be considered if patients are still hyperthyroid 4 months after RAI therapy. No complications of therapy were observed other than moderate worsening of ophthalmopathy in 2/13 patients.

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Accepted 14 Mar 1999.