Research Article

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# Efficacy of Fixed High Dose Radioiodine Therapy for Hyperthyroidism – a 14 year Experience: A focus on Influence of Pre-treatment Factors on Outcomes

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**ABSTRACT**

**Background:** Radioiodine therapy (RAI) is commonly used as a definitive treatment for hyperthyroidism. However there is no agreement on the regime or the dose of RAI used and success rate is quite variable. In addition, the literature on the factors governing the success of the initial dose is conflicting.

**Objective:** We have adopted a standard 550 MBq dose for all patients with hyperthyroidism. The aims of our study were (1) to assess the success rate of this regime in terms of cure of hyperthyroidism and (2) to evaluate the role of pre-treatment factors including age, gender, use of antithyroid medication prior to RAI, aetiology of hyperthyroidism and free thyroxine levels at diagnosis, as predictors of response to RAI.

**Patients and methods:** The study is a retrospective analysis of 584 patients treated at this centre over a 14 year period. All patients received a fixed 550MBq dose following withdrawal of antithyroid medication for 7 days. Repeat dose was administered if patients remained hyperthyroid at the end of one year after the initial dose. Success rate in terms of cure of hyperthyroidism was calculated. The association of pre-treatment factors and failure to respond to the first dose of RAI was studied using univariate and multivariate analyses.

**Results:** Mean age was 56 years (range 20-90 years) with female preponderance (82%). Of the 478 patients in whom the aetiology could be ascertained by the criteria used, 344(72%) patients had Graves' disease and 134(28%) patientshad toxic nodular disease. At the end of one year 545(93%) patients were either hypothyroid (411(70%)) or euthyroid (134(23%)) and were considered to be cured, while 39(7%) patients remained hyperthyroid and required further doses of RAI. Free thyroxine level at the time of diagnosis was the only pre-treatment factor, which independently influenced post-RAI outcome and a higher free thyroxine level predicted a lower cure rate.

**Conclusion:** A standard 550MBq dose of RAI has a low failure rate when used for the treatment of hyperthyroidism. In our experience, only high free thyroxine levels at diagnosis was associated with a lower cure rate.

## Introduction

Hyperthyroidism is one of the most frequently encountered conditions in clinical endocrinology.[1] The modes of treatment available are antithyroid drugs, surgery and radioiodine (RAI) and although each of these is highly successful in controlling or curing hyperthyroidism none leads to permanent euthyroidism on a consistent basis. [2] Although over the last three decades RAI therapy has replaced surgery as the leading form of definitive treatment [3, 4, 5] there is no universally accepted dose or regime for its use. Previous attempts to individualise the dose of RAI to reduce the rate of post-RAI hyper- or hypothyroidism have been unsuccessful [6, 7]. Fixed dose RAI administration has therefore become the most commonly used regime although the actual dose of RAI used varies considerably and ranges between 185MBq to 600MBq [8, 9]. For the last two decades we have used a fixed RAI dose of 550MBq for all patients. Others have used this regime with a high success rate [10] and a prospective head to head comparison with the calculated dose method found the fixed dose regimen to be superior for curing Graves' hyperthyroidism [11].

Conflicting results have been produced in several studies that have attempted to predict outcome following RAI therapy by correlating cure rate with various pre-treatment factors including age, gender, aetiology of hyperthyroidism, goitre size, use of antithyroid drugs, free thyroxine levels at diagnosis and thyroid antibody status. Various forms of calculated or low fixed dose RAI therapy have been used in these studies but no study used a high fixed dose of 550MBq. In this study we have evaluated the overall success rate of high fixed dose RAI therapy and attempted to identify simple clinical predictors of failure to respond the initial RAI dose.

## Patients and Methods

The study is a retrospective analysis of 584 consecutive patients referred to the Shropshire endocrinology service (Princess Royal Hospital and Royal Shrewsbury Hospital) over a 14 year period for the treatment of hyperthyroidism. These patients received RAI therapy at Royal Shrewsbury Hospital, which is the only centre providing facilities for RAI administration in the county of Shropshire and also draws referral from adjoining trusts in Powys, North Wales. Information for this study was obtained from the thyroid database which is maintained on all patients who have received RAI since 1985 at the above hospitals.

RAI was administered both as a primary (53%) and as secondary (47%) treatment. A majority of patients with moderate to severe hyperthyroidism were rendered euthyroid by antithyroid drugs (ATD). Ninety percent (518/584) patients were pre-treated to euthyroidism by antithyroid drugs (carbimazole in 95% and propylthiouracil in 5%) before RAI therapy. Carbimazole was withdrawn one week and

propylthiouracil 4 weeks prior to RAI therapy. A standard RAI dose of 550MBq was administered to all patients without a prior uptake study. Thyroid function was measured at 6 weeks and at 3, 6 and 12 months following RAI therapy. ATD drugs were not recommenced routinely following RAI therapy and were reserved for patients who were persistently and significantly hyperthyroid following RAI administration. Patients who developed clinical and biochemical hypothyroidism after the initial 6-8 weeks were commenced on thyroxine. Patients with high free thyroxine level (FT4) and a suppressed thyroid stimulating hormone (TSH) level and those on antithyroid medication were defined as being hyperthyroid, those with low FT4 or on thyroxine as hypothyroid and those with normal FT4 and a normal or low TSH as euthyroid. At the end of one year if a patient remained hyperthyroid, another RAI dose of 550MBq was administered. The patient was considered to have been "cured" if euthyroidism or hypothyroidism was achieved during the first year following RAI therapy and "not cured" if patient remained persistent hyperthyroidism at the end of this period.

Information recorded on the database included age, gender, aetiology, indication (primary or secondary), dose of RAI, number of RAI doses, name and duration of antithyroid drugs used, if any, and FT4 and TSH levels at diagnosis, at the time of RAI therapy and at 6 weeks, 3, 6 and 12 months after RAI therapy. Diagnosis of Graves' disease was based on the presence of Graves' ophthalmopathy or a combination of a diffuse goitre and a significant titre of thyroid peroxidase antibodies or if radionuclide scan showed diffuse uptake. Toxic nodular disease was diagnosed on the grounds of a nodular goitre and a focal increase in radionuclide uptake. Patients who could not be classified to either of the groups on clinical grounds and where a radionuclide scan could not be performed for a variety of reasons, were categorised as "unclassified" on aetiological grounds.

**Statistical analysis**

Continuous random variables were compared using t-tests and association of categorical variables by using chi-squared tests. The effect on outcome (cure of hyperthyroidism) of all variables was assessed by using logistic regression analysis and a step-wise routine was applied to choose the best set of predictors. All analyses were carried out by using NCSS2000.

**Results**

Data on 584 patients was included with a mean age of 56 years (range 20-90) and a female preponderance (82%). Assessment of the aetiology of hyperthyroidism was made by the above-mentioned criteria. In 110(15%) patients precise aetiological diagnosis could not be made. 344/474 (72%) patients had hyperthyroidism secondary to Graves' disease and 134/474(28%) had toxic nodular disease. 518 patients received pre-RAI antithyroid medications. Mean free thyroxine level at time of diagnosis was 45.4pmol/L in 259 patients in whom this information was available. Data for thyroid status at 3, 6, and 12 months post-radioiodine were available in 97, 94 and 100% patients respectively (see Table 1).

Table 1: Thyroid status at 3, 6 and 12 months

| | Euthyroid (%) | Hypothyroid (%) | Hyperthyroid (%) |
|---|---|---|---|
| 3 months | 308 (54%) | 176 (31%) | 87 (15%) |
| 6 months | 210 (38%) | 280 (51%) | 59 (11%) |
| 12 months | 134 (23%) | 411 (70%) | 39 (7%) |

FT4 values were entered onto the database more recently and this result was available in 259 patients. The group of patients where FT4 data was available was comparable to the group where this information was not available in all respects apart from age (mean age (SD) 54 (±15) vs 58 (±14) years respectively, $p<0.02$). Similarly, the group of patients in whom the aetiology could not be ascertained was not different from the group where the aetiology could be identified in any respect apart from the age (mean age (SD) 60 (±13) vs 55 (±15) respectively).

Table 2 – Forward Stepwise (Wald) logistic regression analysis to identify factors independently associated with failure to respond to first dose of RAI

| Variables | P value | Adjusted r2; OR (95% CI) |
|---|---|---|
| Free T4 at diagnosis | 0.005 | 0.084; 1.04 (1.01-1.07) |
| Free T4 > 45 pmol/l at diagnosis* | 0.02 | 0.056; 3.43 (1.17-10.04) |
| Age | 0.81 | N/A |
| Gender | 0.18 | N/A |
| Aetiology | 0.23 | N/A |
| Pre RAI use of anti-thyroid drugs | 0.42 | N/A |

* Regression analysis carried out with free T4 as a continuous variable and separately as a categorical variable at a cut off of 45pmol/l

One year following RAI treatment, 543(93%) patients were either euthyroid (162;28%) or hypothyroid (383;65%) and considered "cured"; 39(7%) patients remained hyperthyroid and required further doses of RAI, with 34(6%) patients requiring two doses and 5(1%) patients three doses. At 3 months, 484 out of 571 (85%) patients, and at 6 months, 490 out of 549 (89%) patients were "cured" (table 2). On univariate analysis no correlation could be established between the failure to respond to the first dose RAI and age, gender, aetiology or use of antithyroid medication ($p$ = ns for all) although the rate of hypothyroidism was significantly higher at the end of one year in patients with Graves' disease as compared to those with toxic nodular disease (77.1% vs. 50.3%, $p<0.01$). These results were not affected by limiting the analyses to any of the following groups: only those patients in whom the aetiological diagnosis could be made (n=478), only those patients in whom FT4 value was available (n=259) or only those patients where

both FT4 was available and aetiology could be ascertained (n=209). On univariate analysis FT4 at diagnosis was associated with the outcome when it was used as a continuous variable ($p<0.05$) or as a categorical variable with the cut off set at mean FT4 value of 45pmol/L ($p=0.01$) and high values were associated with failure to respond to the first dose of RAI (mean ± SD, 57.28±20.1 v 44.58±16.1 pmol/L, $p<0.05$). On multivariate analysis with all variables, FT4 was found to be independently associated with outcome and again this association was seen when FT4 was used as a continuous variable ($p=0.01$) as well as a categorical variable ($p=0.02$). On using step-wise selection routine only FT4 could be chosen as a predictor when criterion for selection was set at $p=0.05$ and a value of over 45pmol/L predicted failure to respond to the first dose of RAI.

**Discussion**

The use of a standard fixed-dose RAI therapy is gaining increasing popularity and several studies have now shown that formal estimation of the required dose based on the thyroid size and iodine kinetics does not lead to a higher cure rate[6,7,10,11] or a lowerhypothyroidism rate [7]. For several years we have used 550MBq dose for all patients of hyperthyroidism. The overall success rate with this regime was 93% and only 7% of patients required a repeat RAI dose. These figures are comparable to those from most other centres, which have used a similar dose of RAI [10]. In addition to achieving a high cure rate, hyperthyroidism was controlled rapidly with 85% of the patients becoming either euthyroid or hypothyroid within 3 months of treatment. Early onset of hypothyroidism (>70% at 12 months) facilitated institution of thyroxine replacement therapy during the first year during which the patients were being closely followed.

The use of a relatively higher dose of RAI leads to more stringent restrictions to the normal life of patients and these have to be followed for a longer period of time than is the case with the use of a lower dose. Majority of patients accept these restrictions at the prospect of a cure of hyperthyroidism. However, even at this dose, 7% of patients required repeat dosing which in turn led to another restrictive period for these patients. In view of this it is useful to be able to predict failure of the first dose in an individual patient. This would enable us to warn these patients about the higher possibility of requiring repeat dosing, further period of post-RAI restrictions and target them for a closer follow up. To allow us to make this prediction we correlated simple clinical pre-treatment variables to the need for repeat dosing. We found that there was no statistically significant correlation between age, gender, aetiology and the use of anti-thyroid medication prior to RAI and the outcome following RAI therapy although a high free thyroxine level at diagnosis predicted a failure of the first dose to achieve a cure of hyperthyroidism. There are several conflicting reports in the literature on the correlation between these factors and the response to RAI therapy. Most of the studies have failed to show a significant association between the age of the patient and the outcome irrespective of whether the age was used as a continuous or a categorised variable [12-15] although in a study where a standard 150 gray RAI was used age >50 was found to be associated with a higher failure rate [16]. In one study, male gender was associated with a lower cure rate following a single dose of RAI in patients with Graves' disease [12] although others have failed to confirm this association [13,14]. Use of antithyroid drugs prior to RAI has been shown to independently reduce the success rate of RAI [17, 18] while other studies have shown such an association with the use of propylthiouracil but not with carbimazole[19, 20]. Literature on the association between the aetiology of hyperthyroidism and the outcome is even more confusing. Patients with toxic nodular disease have been considered to be more radio-resistant as compared to patients with Graves' disease [21] although opposite results have also been noted [22]. In other studies no correlation could be established on multivariate analysis between the aetiology and outcome following RAI [14, 18]. Our study is the only one which analyses the influence of these factors on the outcome following the use of a standard 550MBq RAI dose and the above studies which have attempted to identify clinical predictors of outcome have either used various forms of the calculated dose regime or a lower fixed-dose RAI regime. We feel that this is the reason for the inconsistencies in the results and when a 550MBq dose RAI is used only FT4 value at diagnosis could predict the failure of RAI therapy to achieve cure. This dose of RAI appears to override the variations in the response induced by the remaining pre-treatment variables studied.

Studies using smaller doses or calculated doses of RAI have shown the outcome to be inversely associated with the thyroid size [14, 16] although this could not be ascertained in our study due to the lack of consistent documentation of the size ofgoitre in the clinical notes. In addition there are several possible confounding factors. Firstly the overall cure rate could have been influenced by the long period of time over which patients have been included (15 years) and the resulting changes in the criteria and threshold for the use of RAI. However if we divide the figures into 3 time periods of 5 years each, the findings remain consistent during each of these periods. Secondly, in over 50% of our patients, RAI was administered as a primary measure and it could be argued that a larger number of patients with milder hyperthyroidism may have been included in our cohort as compared to the patients at other centres where RAI is mainly reserved for patients who fail to respond to ATD. However there was no significant difference in the cure rate between those patients who received RAI as a primary measure and those in whom RAI was administered as a secondary treatment (94% v 93%). Thirdly in 15% of patients the aetiology could not be ascertained by using our well-defined criteria, mainly because of the practical difficulty of performing radionuclide scans in some of the patients where the diagnosis could not be made clinically. We do not feel that our results on the association between the aetiology and the cure rate were affected, as the patients with undefined aetiology were

comparable to the remaining patients in all respects apart from age and had similar outcomes. Lastly the information on the FT4 value at diagnosis was available in only 259 patients. To exclude a selection bias this group was compared to the group of patients where this information was not available. Again the only difference between the two groups was the age distribution. In both instances this difference was not large (though statistically significant) and we do not feel it affected the outcome, especially as age does not appear to influence the outcome following RAI therapy. We could not assess the impact of post-RAI use of antithyroid drugs as these were not routinely restarted following RAI therapy at our centre.

In conclusion, high fixed dose RAI therapy is a very effective treatment for patients with hyperthyroidism and has a high success rate. Failure to respond to this dose cannot be predicted by most of the pre-treatment variables apart from the severity of the hyperthyroidism as judged by the FT4 value at diagnosis. Patients who present with severe hyperthyroidism should be warned regarding the higher possibility of requiring further doses of radioiodine even when treated with a dose of 550MBq.

**Competing Interests**
None declared
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