Outcome of $^{131}$I therapy in hyperthyroidism using a 550MBq fixed dose regimen

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Accepted 30 January 2013

Summary

Background: Radioiodine is the treatment of choice for relapsed hyperthyroidism although the optimum protocol is uncertain. Fixed dose radioiodine is increasingly popular but responses may vary.

Aim: To assess the outcome of $^{131}$I therapy in hyperthyroidism using a standard dose regimen in a regional referral centre and to explore factors influencing outcome.

Methods: We studied 449 patients (M:F 82:367; age range 13-89y, median 42y) with hyperthyroidism treated between 2003 and 2007 with a standard dose of 550MBq $^{131}$I. Patients were classified as either Graves’ disease, toxic multinodular goitre or indeterminate aetiology. Antithyroid drugs were routinely stopped at least 1 week before radioiodine.

Results: One year after radioiodine 334 (74%) were hypothyroid, 85 (19%) were euthyroid and 30 (7%) had required a further dose of $^{131}$I. Patients with Graves’ disease were more likely to become hypothyroid than those with toxic multinodular goitre (78% v 37%, p<0.001) and less likely to become euthyroid (11% v 55%, p<0.001). Free T4 >80pmol/L (normal range 9.0 – 19.0 pmol/L) at presentation was associated with an increased failure rate (17% compared with 5% and 3% for 40-79pmol/L and <40pmol/L respectively; p=0.01). Patients with either a small or no goitre were more likely to be successfully treated by a single dose (96%) than those with a medium/large goitre (85%, p<0.001). Anti-thyroid medication was taken by 345 (77%) (carbimazole n=319) patients up to 1 week prior to $^{131}$I and was associated with an increased failure rate (8% v 2%, p=0.027) compared to those who had not had antithyroid medication. Logistic regression showed free T4 at presentation to be the only independent risk factor for failure of the first dose of radioiodine (OR 2.5; 95% CI, 1.2-5.1, p=0.012).

Conclusion: A single standard dose of 550MBq $^{131}$I is highly effective in treating hyperthyroidism. The aetiology, severity of hyperthyroidism at diagnosis, goitre size and prior antithyroid medication all had a significant effect on outcome.

Keywords: Radioiodine, hyperthyroidism,
not on replacement therapy have an increased mortality risk compared to those on adequate replacement.5

In the present study we assessed the effects of a 550MBq standard dose regimen for the treatment of hyperthyroidism. We also explored clinical factors previously suggested to influence outcomes such as age, gender, goitre size and severity of hyperthyroidism.11,12,15

METHODS
We performed a case note study of 449 consecutive patients treated with 131I for hyperthyroidism between 2003 and 2007 at the Royal Victoria Hospital. Patients had either been referred by their general practitioner with relapsed hyperthyroidism or had already been attending our centre for treatment of their initial episode of hyperthyroidism. Data was retrieved by a single investigator (ASL).

Age and thyroid function at initial presentation were defined as the patient’s age and thyroid function when abnormal thyroid function was documented for the first time. Graves’ disease was classified as biochemical hyperthyroidism accompanied by 2 of the following 3 criteria: a diffuse goitre, a significant anti-TPO antibody titre and dysthyroid eye disease. Toxic multinodular goitre was diagnosed either by clinical examination or if a multinodular goitre was confirmed by ultrasound scanning; ultrasound scanning was not performed routinely. Aetiology was classified as indeterminate if either of these criteria were not met. Presence of goitre was assessed clinically by one of six endocrinologists (ABA, PMB, CHC, DRM, KM, SJH) and documented as either none, small, medium or large. Eye signs were defined according to the NOSPECS classification and recorded as either present or absent at the time of radioactive dose. The use of steroid cover for 131I in those with documented dysthyroid eye disease was also recorded. Our policy was not to use radiiodine unless the dysthyroid eye disease had been established to be stable. The use of antithyroid medication prior to radiiodine was defined as antithyroid medication (carbimazole or propylthiouracil) started following relapse of hyperthyroidism. All antithyroid medication was stopped at least 1 week before radiiodine administration. Patients on combination therapy with antithyroid drugs and thyroxine had their thyroxine stopped 4 weeks before radiiodine.

A fixed dose of 550 MBq was administered and patients subsequently attended standardised follow-up at the endocrine specialist nurse led clinic at 6 and 12 weeks and then as required before attendance with an endocrinologist at 6 months. Thyroid function, recorded during each of these visits, was retrieved and yearly data were obtained from the patient chart, the hospital laboratory results computer system or the general practitioner records. Outcome of therapy was recorded as: 1) hypothyroid defined as low free T4, and high TSH requiring thyroxine replacement, 2) euthyroid defined as normal thyroid function off all thyroid medication at 1 year post radiiodine, or 3) required further radiiodine defined as a relapsing high free T4, and suppressed TSH.

Statistical analysis was performed using SPSS version 15.0. The χ² test was used to test for associations between categorical variables and independent samples t test was used for relationship between continuous variables. Logistic regression was used to determine which factors contributed to the prediction of outcome of treatment.

RESULTS
The demographic and clinical details of the patients at presentation are in table 1. One hundred and one patients (22.5%) were classified as having Graves’ disease, 75 (16.7%) had toxic multinodular goitre and the remaining 273 patients (60.8%) were classified as indeterminate aetiology. Patients with Graves’ disease were younger (40.0 v 57.2y, p<0.001) and had higher free T4 at presentation than the patients with toxic multinodular goitre. All patients had eye status documented and 39 patients (8.7%) had dysthyroid eye disease at the time of 131I. Of these patients 87.2% had steroid therapy across 131I treatment. The remainder had burnt out disease. Prior use of antithyroid medication occurred in 345 patients (76.8%). There was no significant difference noted in T4 levels or goitre size in those who were on prior antithyroid medication and those who were not.

One year after radiiodine, 334 patients (74.4%) were hypothyroid, 85 (18.9%) were euthyroid and 30 (6.7%) had required a further dose of radiiodine (table 2). Hypothyroidism was more likely to occur in Graves’ disease patients than in those with multinodular goitre (78.2% v 37.3%, p<0.001) and euthyroidism was less likely (10.9% v 54.7%, p<0.001) (table 2). There was no significant difference in the numbers requiring a further dose of radioiodine. Patients with indeterminate aetiology had similar outcomes to the Graves’ disease patients with 83.2% hypothyroid, 12.1% euthyroid and a slightly lower figure of 4.8% requiring a further dose of radiiodine.

A high free T4 at presentation was associated with an increased failure rate of radiiodine. Those presenting with an initial free T4 >80pmol/L were found to have an increased failure rate compared to those presenting with an initial free T4 of 40-79pmol/L or <40pmol/L respectively (16.7% v 5.0%, p=0.003). More of those presenting with a medium or large goitre required a further dose of radiiodine than those with a small or no goitre (14.7% v 4.3%, p<0.001). More of the patients who were on antithyroid medication required a second dose of radioiodine than those who were not (8.1% v 1.9%, p=0.027).

Gender did not influence the outcome nor was there any gender association with initial free T4 or aetiology of hyperthyroidism. Females were however more likely to have a positive family history of thyroid dysfunction (52.5% v 37.3%, p=0.025) although this did not influence outcome. There was no association between cigarette smoking and outcome of radioiodine therapy.
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Logistic regression analysis was performed with the inclusion of free $T_4$, goitre size and prior antithyroid medication. It showed initial free $T_4$ at presentation to be the only independent risk factor for failure of the first dose of radioiodine (OR 2.5; 95% CI, 1.2-5.1, $p=0.012$). The influence of goitre size was not significant in the logistic regression model with the inclusion of free $T_4$ at presentation. Prior antithyroid drug use also lost significance in the logistic regression model (OR 5.5; 95% CI, 0.7-43.1, $p=0.10$). Further analysis suggested the reason for this may be the reduced number of patients with free $T_4$ levels available (n=257) rather than an interaction between free $T_4$ and prior antithyroid drug use.

**DISCUSSION**

The use of radioiodine for hyperthyroidism has increased\(^\text{17}\) with recognition of the low likelihood of success with antithyroid drugs. Initially the focus of $^{131}$I therapy was to achieve euthyroidism utilising low/adjusted dose regimens\(^\text{18-20}\) however it is now recognised that the development of hypothyroidism is progressive, with an annual incidence of 2-3% many years after therapy.\(^\text{21}\) Many clinicians now prefer to give a large ablative dose of $^{131}$I which results in early hypothyroidism and prompt stabilization with longterm thyroid hormone replacement. Various clinical factors may influence the outcome of $^{131}$I therapy and knowledge of these can help inform patients prior to treatment and can aid follow-up planning. In this study 93.3% were treated effectively by a single dose of radioiodine with 74.4% rendered hypothyroid and 18.9% euthyroid at one year. These levels compare favourably with similar fixed dose regimens which described cure rates of up to 84.5% with comparable radioiodine doses.\(^\text{11,12}\)

Graves’ disease patients were more likely to be rendered hypothyroid than those with toxic multinodular goitre and those with toxic multinodular goitre were more likely to be rendered euthyroid. This concurs with other published data which have shown a similar relationship even years after initial radioiodine administration.\(^\text{11,22-25}\) One explanation for this could be that suppressed extranodular thyroid tissue exhibits less uptake of radioiodine and continues to function normally after ablation of the nodal tissue.\(^\text{14}\) A recent study showed that in toxic nodular goitre TSH levels at the time of radioiodine dose influenced outcome of radioiodine therapy; higher levels were associated with increased rates of hypothyroidism. This was thought to be due to the suppression by antithyroid medication of the autonomous nodules to a near euthyroid state allowing the remainder of the gland being able to take up radioiodine and therefore subsequently leading to an increased risk of hypothyroidism.\(^\text{22}\)

Previous studies have shown both goitre size and severity of hyperthyroidism to be independent indicators of response to radioiodine therapy\(^\text{11,12}\) but this study found severity of hyperthyroidism to be the only independent factor with goitre size losing significance indicating a relationship between the two. Increased failure rate of radioiodine was associated with free $T_4 >80$pmol/L at presentation (16.7%). It was also seen with medium or large goitres but this was not statistically significant in the logistic regression model. It should be acknowledged that goitre size was determined clinically by one of 6 consultant endocrinologists rather than by an objective measurement. Some inter-observer variability would be expected in this setting and should be acknowledged.

Prior use of antithyroid medication was initially found to be associated with an increased failure rate of radioiodine in univariate analysis but this was no longer significant in the logistic regression model. This may be a result of reduced numbers of free $T_4$ levels available for analysis rather than any interaction between the two variables. Antithyroid medication is used to diminish symptoms while awaiting radioiodine and to reduce the risk of acute hyperthyroidism, including thyroid storm, following radioiodine therapy.\(^\text{28}\) By treating hyperthyroidism with medication, uptake of radioiodine in the thyroid can be reduced with loss of potential effect. Previous studies found increased failure rates with prior antithyroid medication and also increased frequency of hypothyroidism in those who were successfully treated,\(^\text{29}\) a finding confirmed by the current data. These studies contrast with that of Allahabadia et al who found that antithyroid medication taken within two weeks of radioiodine did not significantly affect outcome when doses of 370MBq or more were used.\(^\text{11}\) We have no explanation for this discrepancy.

Our study did not take into account the recognised phenomenon of transient hypothyroidism.\(^\text{27}\) A retrospective study from Japan studied 260 patients with Graves’ disease treated with radioiodine in the preceding 1-15 years. It identified 39 patients (15%) with transient hypothyroidism, 33 (84.6%) of whom were euthyroid at one year and the other 6 (15.4%) were hyperthyroid.\(^\text{28}\) Rates of transient hypothyroidism range from 9-17%.\(^\text{6,29,30}\) Given that our patients with radioiodine induced hypothyroidism were not given a trial period off thyroxine it is possible that a proportion were wrongly labelled as hypothyroid. We would not, however, expect this to alter the failure rate of radioiodine as patients relapsing, even from an initial hypothyroid state, would be expected to do so within a year of treatment. A study at 1 year of brief withdrawal of thyroxine to ensure the presence of hypothyroidism would answer this question and be a valuable addition to the literature.

In conclusion we have demonstrated that a fixed dose of $^{131}$I 550MBq is highly effective in the treatment of hyperthyroidism. A standard fixed dose is a simple and relatively inexpensive method of radioiodine administration which avoids the need for thyroid ultrasound or iodine uptake scans and reduces the need for repeated doses of $^{131}$I. In addition it achieves rapid resolution of hyperthyroidism and simplifies follow-up. In our case we have used a structured specialist nurse led clinic in the early months and this has proved invaluable. Knowledge of the presenting free$T_4$, which we were not always able to obtain, has shown that a
level >80 pmol/L is the most important prognostic indicator of relapse and can be used to inform clinicians of the likely requirement of repeated doses of radioactive iodine or alternatively, and in our view preferably, the use of a higher initial dose in these patients.

The authors have no conflict of interest

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