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Paper

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

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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 131I 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 131I. 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 131I. 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 131I 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 131I 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,

INTRODUCTION

Hyperthyroidism is a common condition which may be associated with significant morbidity.[1] Cardiovascular morbidity secondary to hyperthyroidism is more common in the elderly and includes atrial fibrillation and congestive heart failure.[2-5] Hyperthyroidism may also contribute to increased all cause and circulatory mortality.[6,7] It is therefore important that hyperthyroidism is treated promptly and effectively to minimise adverse outcomes.

Radioiodine is a safe and effective management option in hyperthyroidism although there is no clear consensus regarding its use. In the United States ^{131}I is often recommended first line whereas in Europe it is the treatment of choice for relapsed hyperthyroidism.[8] There is also variation in ^{131}I dosages used between centres. Studies investigating the role of variable dose ^{131}I administration through initial assessment and dose calculation with ultrasound and radioiodine uptake have been performed but have shown no clear advantage of dose adjustment over fixed dose regimens with regard to final outcome of radioiodine treatment.[9,10] Various fixed dose regimens have been employed with higher doses of radioiodine being associated with improved outcomes and lower failure rates.[11-13] These fixed dose regimens are less expensive as estimation of gland size by ultrasound or radioiodine uptake scan prior to treatment is not required.[9,14]

The aim of ^{131}I treatment varies between centres although many now target hypothyroidism as opposed to euthyroidism as this reduces the risk of late onset hypothyroidism.[14] There is some evidence that following radioiodine, euthyroid patients not requiring levothyroxine and hypothyroid patients

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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 ^{131}I for hyperthyroidism between 2003 and 2007at 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[16] classification and recorded as either present or absent at the time of radioiodine dose. The use of steroid cover for ^{131}I in those with documented dysthyroid eye disease was also recorded. Our policy was not to use radioiodine unless the dysthyroid eye disease had been established to be stable. The use of antithyroid medication prior to radioiodine was defined as antithyroid medication (carbimazole or propylthiouracil) started following relapse of hyperthyroidism. All antithyroid medication was stopped at least 1 week before radioiodine administration. Patients on combination therapy with antithyroid drugs and thyroxine had their thyroxine stopped 4 weeks before radioiodine.

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 T_4 and high TSH requiring thyroxine replacement, 2) euthyroid defined as normal thyroid function off all thyroid medication at 1 year post radioiodine, or 3) required further radioiodine defined as a relapsing high free T_4 and suppressed TSH.

Statistical analysis was performed using SPSS version 15.0. The χ^2 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 T_4 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 ^{131}I. Of these patients 87.2% had steroid therapy across ^{131}I 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 T_4 levels or goitre size in those who were on prior antithyroid medication and those who were not.

One year after radioiodine, 334 patients (74.4%) were hypothyroid, 85 (18.9%) were euthyroid and 30 (6.7%) had required a further dose of radioiodine (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%, $p<0.001$)(table2). 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 radioiodine.

A high free T_4 at presentation was associated with an increased failure rate of radioiodine. Those presenting with an initial free T_4 >80pmol/L were found to have an increased failure rate compared to those presenting with an initial free T_4 of 40-79pmol/L or <40pmol/L respectively (16.7% v 5.0% v 2.9%, $p=0.003$). More of those presenting with a medium or large goitre required a further dose of radioiodine 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 T_4 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.

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[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[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.[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.[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.[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.[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.[22]

Previous studies have shown both goitre size and severity of hyperthyroidism to be independent indicators of response to radioiodine therapy[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 >80pmol/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.[26] 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,[26] 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.[11] We have no explanation for this discrepancy.

Our study did not take into account the recognised phenomenon of transient hypothyroidism.[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.[28] Rates of transient hypothyroidism range from 9-17%.[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[31] 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 freeT_4, which we were not always able to obtain, has shown that a

level >80pmol/L is the most important prognostic indicator of relapse and can be used to inform clinicians of the likely requirement of repeated doses of radioiodine or alternatively, and in our view preferably, the use of a higher initial dose in these patients.

The authors have no conflict of interest

REFERENCES

1. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, *et al.* The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol.* 1977; **7(6):** 481-93.
2. Cobler JL, Williams ME, Greenland P. Thyrotoxicosis in institutional elderly patients with atrial fibrillation. *Arch Int Med.* 1984; **144(9)**: 1758-60.
3. Trivalle C, Doucet J, Chassagne P, Landrin I, Kadri N, Menard JF, *et al.* Differences in the signs and symptoms of hyperthyroidism in older and younger patients. *J Am Geriatr Soc.* 1996; **44(1)**: 50-3.
4. Shimzu T, Koide S, Noh JY, Sugino K, Ito K, Nakazawa H. Hyperthyroidism and the management of atrial fibrillation. *Thyroid.* 2002; **12(6)**: 489-93.
5. Franklyn JA, Sheppard MC, Maisonneuve P. Thyroid function and mortality in patients treated for hyperthyroidism. *JAMA.* 2005; **294(1)**: 71-80.
6. Franklyn JA, Maisonneuve P, Sheppard MC, Betteridge J, Boyle P. Mortality after the treatment of hyperthyroidism with radioactive iodine. *New Engl J Med.* 1998; 338(11): 712-8.
7. Völzke H, Schwahn C, Wallaschofski H, Dörr M. The association of thyroid dysfunction with all-cause and circulatory mortality: is there a causal relationship? *J Clin Endocrinol Metab.* 2007; **92(7)**: 2421-9.
8. Wartofsky L, Glinoer D, Solomon B, Nagataki S, Lagasse R, Nagayama Y, *et al.* Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. *Thyroid.* 1991; **1(2)**: 129-35.
9. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. *J Clin Endocrinol Metab.* 2003; **88(3)**: 978-83.
10. Jarløv AE, Hegedüs L, Kristensen LØ, Nygaard B, Hansen JM. Is calculation of the dose in radioiodine therapy of hyperthyroidism worth while? *Clin Endocrinol.* 1995; **43(3)**: 325-9.
11. Allahabadia A, Daykin J, Sheppard MC, Gough SCL, Franklyn JA. Radioiodine treatment of hyperthyroidism – prognostic factors for outcome. *J Clin Endocrinol Metab.* 2001; **86(3)**: 3611-7.
12. Boelaert K, Manji N, Sheppard M, Gough S, Franklyn JA. Using an increased fixed dose of ^{131}I (600MBq) leads to improved outcome in patients with hyperthyroidism. *Endocr Abstr.* 2007; **13**: P312.
13. Dalzell G, Atkinson AB, Kennedy L, Hadden DR. Irish Endocrine Society. Proceedings of annual meeting in Cork, October 25th and 26th, 1985. High dose radioactive iodine therapy in the treatment of thyrotoxicosis. *Ir J Med Sci.* 1986; **155**: 339
14. Radioiodine therapy for hyperthyroidism. *Drug Ther Bull.* 2006; **44(6)**: 44-48.
15. Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SCL, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. *J Clin Endocrinol Metab.* 2000; **85(3)**: 1038-42.
16. Werner SC. Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. *J Clin Endocrinol Metab.* 1977; **44(1)**: 203-4.
17. Hart D, Wall BF. A survey of nuclear medicine in the UK in 2003/4. HPA-RPD-003. Health Protection Agency [now Public Health England.] 2005. Didcot, Oxfordshire: Health Protection Agency; 2005. Available online: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947340193. Last accessed March 2013.
18. Bhatia SK, Hadden DR, Montgomery DA, Weaver JA. The management of thyrotoxicosis with therapeutic radioiodine. *Ir J Med Sci.* 1968; **7(10)**: 449-57.
19. Blair ALT, Lowe DC, Hadden DR, Weaver JA, Montgomery DA. Long term follow up of patients treated for hyperthyroidism with low dose radioactive iodine. *Ulster Med J.* 1980; **49(1)**: 71-8.
20. Peters H, Fisher L, Boyner U, Reiners C, Schleusener H. Radioiodine therapy of Graves' hyperthyroidism: standard vs calculated 131iodine activity. Results from a prospective, randomized multicentre study. *Eur J Clin Invest.* 1995; **25(3)**: 186.
21. Tamai H, Kasagi K, Takaichi Y, Takamatsu J, Komaki G, Matsubayashi S, *et al.* Development of spontaneous hypothyroidism in patients with Graves' disease treated with antithyroidal drugs: clinical, immunological and histological findings in 26 patients. *J Clin Endocrinol Metab.* 1989; **69(1)**: 49-53.
22. Adamali HI, Gibney J, O'Shea D, Casey M, McKenna TJ. The occurrence of hypothyroidism following radioactive iodine treatment of toxic nodular goitre is related to the TSH level. *Ir J Med Sci.* 2007; **176(3)**: 199-203.
23. Metso S, Jaatinen P, Huhtala H, Luukkaala T, Oksala H, Salmi J. Long-term follow-up study of radioiodine treatment of hyperthyroidism. *Clin Endocrinol.* 2004; **61(5)**: 641-8.
24. Goolden AW, Davey JB. The ablation of normal thyroid tissue with iodine-131. *Br J Radiol.* 1963; **36(425)**: 340-5.
25. Farrar JJ, Toft AD. Iodine-131 treatment of hyperthyroidism: current issues. *Clin Endocrinol.* 1991; **35(3)**: 207-12.
26. Walter MA, Briel M, Christ-Crain M, Bonnema SJ, Connell J, Cooper DS, *et al.* Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. *Br Med J.* 2007; **334(7582)**: 514.
27. MacFarlane IA, Shalet SM, Beardwell CG, Khara JS. Transient hypothyroidism after iodine-131 treatment for thyrotoxicosis. *Br Med J.* 1979; **2(6187)**: 421.
28. Aizewa Y, Yoshida K, Kaise N, Fukazawa H, Kiso Y, Sayama N, *et al.* The development of transient hypothyroidism after iodine-131 treatment in hyperthyroid patients with Graves' disease: prevalence, mechanism and prognosis. *Clin Endocrinol.* 1997; **46(1)**: 1-5.
29. Connell JM, Hilditch, TE, McCruden DC, Alexander WD. Transient hypothyroidism following radioiodine therapy for thyrotoxicosis. *Brit J Rad.* 1983; **56(665)**: 309-13.
30. Sawers JS, Toft AD, Irvine WJ, Brown NS, Seth J. Transient hypothyroidism after iodine-131 treatment of thyrotoxicosis. *J Clin Endocrinol Metab.* 1980; **50(2)**: 226-9.
31. Franklyn JA. The management of hyperthyroidism. *N Engl J Med.* 1994; **330(24)**: 1731-8.

