The efficacy of low-dose radioactive iodine without a thionamide in the treatment of thyrotoxicosis

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ASTRACT – Between 1999 and June 2001, 55 unselected thyrotoxic patients were prescribed 200 MBq radioactive iodine (^{131}I). None of these patients received a thionamide such as carbimazole or propylthiouracil within two weeks of treatment or subsequently. Symptom relief was achieved using β blockers alone. Remission at one year was achieved in 84% of these patients and of these 62% were hypothyroid and taking thyroxine. Within this time, re-treatment of those who remained thyrotoxic achieved an overall success rate at one year of 95%. The outcome of 164 similar patients prescribed 250–400 MBq ^{131}I between 1996 and 2001 gave comparable results. The failure rate after a single 200 MBq ^{131}I dose was significantly lower than that previously published where 185 MBq ^{131}I and thionamides had been used. Our low-dose strategy has the potential for halving the radiation exposure to the patient and the environment, when compared with the ablative strategies in common use.

KEY WORDS: radioiodine, thionamide, thyrotoxicosis

Introduction

Radioactive iodine (^{131}I) therapy has been used for over 60 years to treat patients with thyrotoxicosis,[1] and in some departments it accounts for 79% of referrals for definitive treatment of adults with this condition.[2] Guidelines formulated by the Royal College of Physicians in 1995 recommended that doses of 300–800 MBq ^{131}I should be used, and that thionamide therapy, such as carbimazole or propylthiouracil, should be given to most patients unless the thyrotoxicosis was mild.[3] Lower doses of ^{131}I were regarded as inadequate, but the outcome in those studies had been compromised by the concomitant use of thionamides,[4–7] which have been shown to reduce the effectiveness of ^{131}I by up to 44%.[8] Doses of 520–555 MBq of ^{131}I will achieve remission rates between 91 and 94% at one year,[9–11] but a clear statement regarding an outcome target is lacking.

It is, however, important to minimise the potential therapeutic hazard of exposing patients and the environment to non-essential radiation. In the light of these considerations, we examined the efficacy of a fixed dose of 200 MBq ^{131}I compared with larger doses, prescribed in our department over the last five years, for thyrotoxic patients whose symptoms were modified by beta-adrenergic blocking drugs alone, and compared our results with the published data.

Patients and methods

From 1996 to June 2001 all thyrotoxic patients referred to the Endocrine Department, and who subsequently received ^{131}I treatment, were entered on our thyroid register. Patients presenting with subacute thyroiditis and those in whom the free thyroxine (FT4) was <22 pmol/l or the thyroid-stimulating hormone (TSH) was detectable, were not considered suitable candidates for ^{131}I treatment. All patients had been given an information package and at a subsequent visit those considered suitable were able to choose from three options: treatment with a thionamide, surgery or ^{131}I.

The dose of ^{131}I prescribed was either 200 MBq or 250–400 MBq. This was given as a ^{131}I capsule. The majority of the patients for whom 200 MBq ^{131}I was prescribed were recruited consecutively after 1999 and without reference to thyroid size, age of the patient or other measures of thyroid overactivity. The activity of each capsule was measured just prior to administration, using a Vinten Isocal isotope calibrator.

Beta blockers were prescribed for all but a few patients, in order to ameliorate symptoms and prevent any exacerbation during the period after the

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Key Points

- **Low-dose ^{131}I therapy is an effective strategy for treating thyrotoxicosis**
- **The use of thionamides to control thyroid overactivity before or after ^{131}I therapy is unnecessary**
- **Symptom control can be achieved with β blockers alone**

^{131}I had been taken. Many patients had had these drugs prescribed before their first clinic visit.

Thyroid size was determined visually and by palpation. Goitres were defined as small if they were impalpable or just visible and palpable when the patient swallowed. Goitres which were more than twice this size were defined as large.

Thyroid status was assessed within 26 and 52 weeks after the initial dose of ^{131}I had been administered and not later than 28 May 2002. Biochemical activity was assessed from measurements of serum TSH and FT_4 by chemiluminescent immunoassay using the Chiron ACS:180® prior to 1998, and by the ADVIA® Centaur™ system thereafter. Both machines employ the same reagents and give closely correlated results.[12]

Where the thyrotoxic state persisted clinically and the FT_4 remained >22 pmol/l and showed no apparent signs of returning to the normal range, or became elevated again after a period of euthyroidism, more ^{131}I was administered. Patients were designated euthyroid when the serum FT_4 had returned to the normal range, even if the TSH was still suppressed, provided that the patient was symptom-free and not reliant on treatment with β blockers. Established hypothyroidism was confirmed after the FT_4 level had fallen below 10 pmol/l and was associated with a TSH greater than 5 mU/l, provided that thyroxine replacement remained necessary in order to maintain the serum TSH at a detectable level.

The significance of our results was assessed using Student's t test and the chi-squared test was used for comparison with published data.

Results

Altogether 227 patients were identified who had chosen ^{131}I as their preferred treatment. Within one year of treatment four patients had left the district and four elderly patients had died of non-thyroid-related disease. These patients were excluded from further assessment leaving a total of 219 subjects who formed the basis for this study. The patients were divided into two groups. Group A comprised those prescribed 200 MBq ^{131}I and group B ≥250 MBq ^{131}I. The demographic details of these patients at the time of treatment are shown in Table 1. A thionamide had been given to 92 patients at some time before the first dose of ^{131}I was administered, but this had been discontinued for at least 14 days prior to treatment, and none of the patients received a thionamide after the ^{131}I had been taken. Disease remission after a single dose of ^{131}I was obtained by 12 months in 84% of patients from group A and 83% from group B (Table 2). In group A, 63% of these responders were hypothyroid compared with 61% in group B, with 37% and 39% becoming euthyroid respectively. Most of the remaining non-responders received more ^{131}I within the 12 months. The overall outcome at 12 months for all 219 patients, irrespective of the number of doses of ^{131}I received, showed that three patients in group A were still toxic, giving a remission rate of 94.5%. This was achieved with a mean dose of 256 MBq. The additional ^{131}I received by these patients varied from 204 to 610 MBq (mean 369 ± 128). Altogether 31 patients from group A were hypothyroid on replacement thyroxine and 21 were euthyroid with the FT_4 within the normal range. In group B six patients remained toxic, giving a remission rate of 95.7%. after a mean dose of 356 MBq. The additional ^{131}I received by these patients varied from 181 to 1,056 MBq (mean 366 ± 182). Altogether 95 patients from group B were hypothyroid on replacement thyroxine and 63 were euthyroid with the FT_4 within the normal range. These outcomes were not significantly different.

Atenolol was used for β blockade in nine patients and the remainder who required symptom modification to an acceptable level took propranolol. The dosage of propranolol required was modest with 120 mg daily as the mode. Few patients with obstructive pulmonary disease were unable to tolerate propranolol whilst

Table 1. Characteristics of all patients studied based on initial dose of ^{131}I administered.

Group (no of patients) ^{131}I dose prescribed	**A** (55) 200 MBq	**B** (164) ≥250 MBq
Mean age (years) (range)	50.5 (23–87)	48.7 (16–94)
Female (%)	40/55 (73)	131/164 (80)
Large glands (%)	11/55 (20)	34/164 (21)
Previous thionamide (%)	20/55 (36)	73/164 (44)
Mean FT_4 – pmol/l (± SD) (range)	44.1 (18.5) (22.3 – 95.4)	45.2 (19.3) (22.2 – 116.6)

Table 2. Outcome within 12 months of first dose of ^{131}I.

Group (no of patients) **Prescribed dose**	**A** (55) **200 MBq**	**B** (164) **≥250 MBq**
Those given one dose ^{131}I (%)	47/55 (85)	140/164 (85)
Mean dose given (MBq) ± SD	196 ± 9	302 ±31
Hypothyroid (%)	29/47 (62)	83/140 (59)
Euthyroid (%)	17/47 (37)	53/140 (38)
Still toxic (%)	1/47 (2)	4/140 (3)
Those given more ^{131}I (%)	8/55 (15)	24/164 (15)
Mean total MBq given ± SD	567 ± 127	661 ± 193
Hypothyroid (%)	3/8 (38)	12/24 (50)
Euthyroid (%)	3/8 (38)	10/24 (41)
Still toxic (%)	2/8 (25)	2/24 (8)
All patients (%)	55 (100)	164 (100)
Those given more ^{131}I (%)	8 (15)	24 (15)
Mean total MBq given ± SD	256 ± 151	356 ± 154
Hypothyroid (%)	32 (58)	95 (58)
Euthyroid (%)	20 (36)	63 (38)
Still toxic (%)	3 (5)	6 (4)

they were thyrotoxic, but the dosage tended to be lower and was withdrawn earlier than in the other patients. No patient developed thyroid storm.

The outcomes of the regimens of other workers, where thionamides had been prescribed after a fixed dose of ^{131}I had been given, are shown in Table 3. Our success rate was comparable to those studies where about twice the dosage had been used.[11,14] Our failure rate after a single dose of 200 MBq ^{131}I was about half that found in other studies where 185 MBq ^{131}I and a thionamide had been administered ($\chi^2 = 6.36, p<0.02$).[9,10]

Discussion

The patients studied in this series were similar in age and sex distribution and goitre size to those reported in other studies.[7] In this series, the outcome for patients who received the lowest doses of ^{131}I was similar to that of patients receiving up to double that dose. Previous studies using small doses of ^{131}I, whilst having a low rate of hypothyroidism, had a low remission rate and relied heavily on controlling the patients' disease by the continuing usage of thionamides.[4–7] We attribute our higher remission rate to the omission of thionamide therapy, since that was the main difference between our series and those of others. Low-dose ^{131}I without a thionamide clearly did not reduce the proportion of patients becoming permanently hypothyroid.

In our hands, β blockers were safe and effective in controlling the patients' symptoms and in that respect a thionamide would have been superfluous.

The omission of a thionamide from the treatment regimen of thyrotoxic patients given ^{131}I appears to be standard practice in some departments. None of the 225 patients from Newcastle treated over a five-year period with an ablative dose of ^{131}I (555 MBq) were given a thionamide, without any complications related to hyperthyroidism being recorded.[9]

The mechanism by which thionamides modify the overactive thyroid gland's sensitivity to ^{131}I is unclear, but is likely to be related to a reduction in the rate at which metabolically active follicular cells are being replaced.

We would agree with the consensus opinion that all thyrotoxic patients should be referred to an endocrine unit at the outset.[15] Our policy is to see all patients within two weeks of referral, and therefore we consider it more appropriate for the referring physician to start a β blocker rather than a thionamide, whilst the patient is waiting to be seen. In this way, ^{131}I therapy need not be delayed unnecessarily should that be the patient's preferred method of treatment.

By using our treatment strategy, the radiation exposure to the patient and the environment can be substantially reduced, and the small risk of fatal thionamide-induced agranulocytosis can be eliminated.

Furthermore, the judicious re-treatment, within one year, of the 16% of patients in whom remission had not been achieved after one dose, produced an overall success rate which was comparable to that achieved by others who give ablative doses of ^{131}I.

Table 3. Treatment success at 12 months where a single fixed ^{131}I dose had been given with a thionamide.

Study	Patients	^{131}I dosage	Hyper-thyroid (%)	Hypo-thyroid (%)
Lowdell *et al* (1985)[5]	164	74 MBq	43	6
Watson *et al* (1988)[6]	199	185 MBq	26	16
Allahabadia *et al* (2001)[7]	443	185 MBq	33	41
Allahabadia *et al* (2001)[7]	370	370 MBq	15	61
Kok *et al* (2000)[14]	30	400 MBq	23	47
Child *et al* (1994)[10]	48	550 MBq	8	67

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