Low-dose ^{131}I in treatment of Graves' disease[1]

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Summary: One hundred and sixty-four patients with Graves' disease were treated with low-dose radioiodine (2 mCi), with a mean follow up of $4\frac{1}{2}$ years. At this time 74 (45%) were euthyroid having had a single dose, with a total of 131 (80%) being controlled with one or more doses. Three (2%) were still toxic but their mean follow up was only 3 years. Thirty (18%) were rendered hypothyroid, two-thirds of these after a single dose of 2 mCi ^{131}I. The one-year incidence of hypothyroidism was 6%, with an incidence at 6 years of 20%. Previous surgery, medical treatment and thyroid antibody status appeared to have no influence on the outcome.

Introduction

Radioiodine has been used in the treatment of thyrotoxicosis since 1942 when it was first reported by Herz & Roberts (1942) and Hamilton & Lawrence (1942). That patients can be treated effectively merely by their having a drink of radioactive iodine on a single occasion remains a major achievement in medicine.

The ideal treatment should render the patient permanently euthyroid by a single noninvasive procedure without any serious side effects. Radioiodine fulfils most of these criteria, but against this one has to balance the delay in achieving control and the incidence of hypothyroidism necessitating life-long replacement therapy. It was Beling & Einhorn (1961) who pointed out that regardless of dose, approximately 3% of patients developed hypothyroidism each year after treatment; the cumulative incidence may be as high as 70% (Nofal *et al.* 1966) within 10 years. Other authors have reported an incidence of only 7% (Glennon *et al.* 1972) 5 years after treatment.

Low-dose treatment is advocated in the expectation that hypothyroidism will be infrequent and that persisting hyperthyroidism can easily be controlled with antithyroid drugs if a second dose of ^{131}I becomes necessary. The alternative approach is for rapid control of toxicity leaving the patient euthyroid, with or without thyroxine replacement therapy, by using large or very large doses of radioiodine.

The incidence of hypothyroidism after ^{131}I therapy appears to be dose-related and various authors have reported favourably low figures one year after treatment with small doses (Smith & Wilson 1967, Cevallos *et al.* 1974, Rapoport *et al.* 1973, Goolden & Fraser 1969, Blair *et al.* 1980). The experience of the Thyroid Unit at the Royal Marsden Hospital with low-dose ^{131}I administration in the treatment of Graves' disease is now described.

Methods

Between January 1972 and December 1978, 345 patients were seen with a diagnosis of thyrotoxicosis. The diagnosis was based on clinical assessment and abnormal thyroid function tests supplemented by 2- and 24-hour uptakes of ^{131}I. Patients selected for ^{131}I were older than 40 years of age or had relapsed after previous treatment with surgery and/or drugs. No

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attempt was made to estimate the weight of the thyroid gland but the size and presence of nodularity were recorded. A total of 158 patients with congestive cardiac failure, multinodular goitre or a solitary hot nodule were given a large dose of 10 mCi ^{131}I and were therefore excluded from the study. The remaining 187 patients were treated with 2 mCi ^{131}I up to December 1978. (For historical reasons the doses of ^{131}I are given in mCi: 2 mCi = 74 MBq, 10 mCi = 370 MBq.)

The age of patients varied from 32 to 81 years (mean 55). There were 148 females and 39 males, giving a sex ratio of 3.8 : 1. All patients on antithyroid medication had this stopped for 3 or 4 days prior to and after ^{131}I administration. Severely toxic patients were instructed to resume both antithyroid medication and beta-blockers following ^{131}I, but modestly toxic patients received beta-blockers only. All patients were reviewed in the outpatient department after 6 weeks and then at 3-monthly intervals, with thyroid function tests being repeated at each visit. Patients were judged to be successfully controlled when clinically euthyroid, off all antithyroid medication and with a normal serum thyroxine and tri-iodothyronine. The diagnosis of hypothyroidism was based on symptoms, signs, laboratory tests and clinical improvement after treatment with thyroxine. If hypothyroidism was suspected, patients were merely observed for some months to ensure that this was not a temporary phenomenon. Patients were considered toxic if they were requiring antithyroid medication or had definite biochemical relapse. ^{131}I therapy was repeated after one year in patients not achieving control. Patients were reviewed at least annually and their final thyroid status is that recorded at the last follow up. Nineteen patients had previous subtotal thyroidectomy and 102 received antithyroid medication prior to referral. The following data were analysed: sex, age, type of goitre, details of previous treatment, 24-hour uptake of ^{131}I, antibody status, number of doses of iodine given and interval from initial diagnosis to radioiodine therapy.

Results

Of 345 cases of thyrotoxicosis treated, 158 received 10 mCi ^{131}I, leaving 187 patients with Graves' disease who received 2 mCi as their initial dose. Of these 187, 23 patients were excluded from analysis for the following reasons: 8 had multinodular goitres on repeated scanning, 6 died from unrelated disease within a year of treatment, 3 were cases of true refractory Graves' disease subsequently treated with 10 mCi ^{131}I, 4 became lost to follow up, one patient submitted to partial thyroidectomy after a single dose of radioiodine, and one patient developed a papillary carcinoma of the thyroid. This left a total of 164 patients treated with 2 mCi who were included in the series. Details of their outcome and the number of doses of ^{131}I required to achieve control are summarized in Table 1.

A total number of 131 (80%) became euthyroid, 74 (45%) after a single dose of ^{131}I. Forty-two (26%) required a second dose, 6 (4%) required a third dose and 9 (5%) required a fourth dose. Three patients (2%) remained toxic although they had a significantly shorter follow up. Thirty (18%) became myxoedematous – 20 of these after receiving only one dose of 2 mCi ^{131}I. In the total study, 96 patients (59%) received a single dose of 2 mCi ^{131}I and 68 (41%) needed more than one dose of 2 mCi ^{131}I, regardless of thyroid status at completion of treatment.

The outcome of 89 patients with a follow up greater than 5 years is shown in Table 2. In 34 (38%) control was achieved after a single dose of 2 mCi ^{131}I. Twelve patients (13%) became hypothyroid after a single dose of 2 mCi ^{131}I and a total of 18 (20%) were hypothyroid after a mean follow up of 6.5 years. This contrasts with an incidence of hypothyroidism of 6% (10/164 patients) found at one year. After one year of follow-up, 91/164 (56%) were euthyroid; 10 of these subsequently relapsed and were given further ^{131}I. Sixty-three patients (38%) were still hyperthyroid at one year.

The influence of previous medical treatment or surgery against no previous treatment is illustrated in Table 3. There are no significant differences between these groups. Of the 19 patients who had previous surgery, 15 (79%) were euthyroid, 10 after a single dose of ^{131}I and 5 after a second dose; the remaining 4 patients (21%) became hypothyroid after a single dose of 2 mCi ^{131}I.

Table 1. Fate of all patients, showing number of 2 mCi doses received and mean length of follow up in years (±s.d.)

	Number of doses of 2 mCi ^{131}I				
	1	2	3	4	Total
Euthyroid					
No. of patients	74 (45%)●	42 (26%)●	6	9	
Follow up (years)	4.5±1.6	5.5±1.7	5.7±2.4	5.0±2.3	131 (80%)●
Hypothyroid					
No. of patients	20 (12%)●	8	1	1	
Follow up (years)	5.1±1.96	5.3±2.43	6	4	30 (18.3%)●
Hyperthyroid					
No. of patients	2	0	1	0	
Follow up (years)	2.5±0.7		6		3 (1.83%)●
Total no. of patients	96	50	8	10	164

●Percentage of total 164 patients

Table 2. Fate of patients with a minimum follow up of 5 years

	Number of doses of 2 mCi ^{131}I				
	1	2	3	4	Total
Euthyroid					
No. of patients	34 (38%)●	29 (33%)●	4	4	71 (80%)●
Follow up (years)					6.2
Hypothyroid					
No. of patients	12 (13%)●	4	1	1	18 (20%)●
Follow up (years)					6.5
Total no. of patients	46	33	5	5	89
Follow up (years) ±s.d.	6.04±1.1	6.5±1.35	6.8±1.5	6.6±0.5	

●Percentage of total 89 patients

Table 3. Patients who received previous treatment or no previous treatment

	No. of doses of 2 mCi ^{131}I				
	1	2	3	4	Total no. of patients
Previous antithyroid drugs	54 (53%)	34 (32%)	6	8	102
Previous subtotal thyroidectomy	14 (74%)	5 (26%)	0	0	19
No previous treatment	23 (53%)	14 (33%)	4	2	43
					164

Information about antibody status was available in 60 patients, 39 (65%) of whom had positive antibodies to thyroid cytoplasmic antigen or thyroglobulin. Titres were recorded as

Table 4. Patients who became euthyroid (131), with number of doses received

	Number of doses of 2 mCi ^{131}I			
	1	2	3	4
No. of patients	74	42	6	9
Mean 24-h ^{131}I uptake	57%	47%	63%	68%
Patients with positive antibody titres	64%	40%	66%	60%
Male : female ratio	1 : 4	1 : 3	0 : 6	1 : 8
Mean age (range) in years	59 (39–78)	56 (35–81)	55 (47–64)	54 (40–77)
Mean no. of years from diagnosis to ^{131}I treatment	4.7	3.7	3.8	8.3

Table 5. Patients who became hypothyroid (30), with number of doses received

Mean 24-h ^{131}I uptake	51%
Patients with positive antibody titres	5/9 (56%)
Male : female ratio	1 : 3.3
Mean age (range) in years	52 (32–75)
Mean no. of years from diagnosis to ^{131}I treatment	3.3
No. of patients by no. of 2 mCi ^{131}I doses received	20 × 1 8 × 2 1 × 3 1 × 4

positive if greater than 1/20. In 26, titres were greater than 100 (ranging from 160–250 to 600). Of the 39 patients with positive antibodies, 32 (82%) became euthyroid, 23 (59%) of these after one dose of 2 mCi ^{131}I (follow up 4.3 years). Six (15.4%) were rendered myxoedematous and one remained toxic. In the group of 26 with strongly positive antibodies there was no increase in the incidence of hypothyroidism, 2 patients becoming hypothyroid after one dose of 2 mCi ^{131}I. The remainder became euthyroid following treatment with one or more doses.

Patients controlled with a single dose of 2 mCi ^{131}I have been analysed in an attempt to identify a group likely to respond best to low-dose therapy (Table 4). The results of the hypothyroid group are compared in Table 5. There are no significant differences between radioiodine uptake figures, antibody status, sex, age or number of years from diagnosis to the initiation of ^{131}I treatment.

Discussion

Hypothyroidism following treatment results from radiation damage to cellular metabolic function (Greig 1965). Its onset is delayed in many patients for several years and in consequence the rate of hypothyroidism increases with length of follow up and even after 15 years shows no signs of a plateau (Dunn & Chapman 1964). The early incidence varies with the dose of ^{131}I used. Conventional therapy aims at a dose of approximately 160 μCu per gram of thyroid tissue. Using 10–18 mCi ^{131}I, Nofal *et al.* (1966) found a one-year incidence of 41%, with 70% of patients becoming hypothyroid within 10 years compared with 43% treated surgically. However, this series consisted of patients with multinodular goitres and solitary nodules as well as Graves' disease. The cumulative incidence of hypothyroidism was 2.8% per year after the first year. Similar figures to these were obtained by Jafiol *et al.* (1980) using a mean first dose of 4.34 mCi. A figure of 20% at one year was obtained by San Marco *et al.*

(1980) using a dose of 6.6 mCi. Dunn & Chapman (1964) showed 25% permanent hypothyroidism at 2 years and Hagen *et al.* (1967) 33% at one year using comparable doses. Best *et al.* (1981) recorded 6% at one year, with an annual incidence of 3.5% thereafter, following a mean dose of 9.9 mCi. Sugrue *et al.* (1980) reported 10% hypothyroidism at 5 years and 30% at 10 years following an average first dose of 7.2 mCi ^{131}I.

However, some results of low-dose therapy have been encouraging. Smith & Wilson (1967) compared the results of a 5 mCi regimen with a 2.8 mCi dose and found that in the latter series 85% of patients were euthyroid at 5 years with only a 7% incidence of hypothyroidism. Rapoport *et al.* (1973), using a mean dose of 2.8–3.8 mCi, found at 54% incidence of persisting toxicity at one year with 7% of patients becoming hypothyroid and 39% euthyroid. They considered the high percentage of toxicity at this time disadvantageous compared with antithyroid drugs alone. Kalk *et al.* (1980), using a low-dose mean 2.8 mCi, found 39% hyperthyroid at one year with 25% hypothyroid. A higher mean dose of 5.9 mCi reduced the rate of persisting thyrotoxicosis to 19% and increased the rate of hypothyroidism by only 4%. Blair *et al.* (1980) compared regimens of 2.5 mCi and 1.25 mCi and found 38% hypothyroid at 7 years and 51% at 10 years in the former, compared with 11.7% at 7 years in the latter group. The mean duration of biochemical hyperthyroidism following treatment was 6.8 ± 7.7 months and 8.5 ± 8.8 months in the two groups respectively. They concluded that the annual incidence of hypothyroidism could be substantially reduced by the use of lower doses of ^{131}I, but that patients remained hyperthyroid longer and were thus subjected to repeated attendances and repeated treatments. They now adopt 2.5 mCi treatments. However, Glennon *et al.* (1972), using low-dose regimens, have reported a 17-year incidence of hypothyroidism of 48% despite a 7.5% incidence at 5 years.

The Royal Marsden Hospital results show an incidence of hypothyroidism of 6% at one year, and 20% at 6.5 years. Of those who eventually became hypothyroid, 66% did so after only one dose. A single dose of 2 mCi ^{131}I was effective as treatment in 57% (94/164) of all cases in that it resulted in euthyroidism in 45% (74/164) and hypothyroidism in 12% (20/164). At 5 years 38% are euthyroid after a single dose of 2 mCi ^{131}I. More than one dose was needed to achieve control in 41% (68/164).

The phenomenon of transient hypothyroidism is well recognized and has been reported in several series. Sawers *et al.* (1980) recorded biochemical evidence of hypothyroidism in 5 out of 30 patients occurring 1–4 months after treatment which recovered spontaneously during the ensuing two months. Others have shown its incidence to vary between 3.5% and 28%. MacFarlane *et al.* (1979) reported 8 cases with transient hypothyroidism recovering within 7 months, none of whom became clinically hypothyroid. They proposed a mechanism similar to that thought to be responsible for transient hypothyroidism occurring after subtotal thyroidectomy, that of a fluctuating titre of thyroid-stimulating immunoglobulins and a delayed recovery of suppressed pituitary thyrotrophs.

In our series, previous medical treatment with carbimazole or surgery does not seem to have had any influence on outcome, in that it did not affect the number of treatments necessary to induce a euthyroid or hypothyroid state compared to those who received no previous treatment. Positive antibody status, and in particular those with high antibody titres, did not seem to be related to a higher incidence of hypothyroidism. This is in contrast to Lundell & Holm (1980) who found a positive correlation between hypothyroidism and the thyroid antibody status both prior to radioiodine treatment as well as in patients who developed thyroid antibodies early after treatment. In the latter group, radioiodine is thought to trigger an autoimmune reaction manifest as an increase in humoral thyroid antibodies.

In the Royal Marsden Hospital study there were no predictive criteria in terms of age, sex, antibody status, 24-hour radioiodine uptake or interval from initial diagnosis for establishing a group of patients who are more likely to respond to low-dose treatment. Nofal *et al.* (1966) found a greater incidence of hypothyroidism in those aged 30–40 years than in patients aged 40–50, with a higher incidence in females and in those with non-palpable glands as opposed to normal size or diffusely enlarged glands. They also found a higher incidence of hypothyroidism in those who had had previous surgery. Patients with multinodular goitres have the lowest

incidence of hypothyroidism (Glennon *et al.* 1972, Greig 1965, Best *et al.* 1981, Hamada *et al.* 1979) but there is no correlation with antibody status. It should be stressed that to reduce the dose of ^{131}I in an attempt to minimize the incidence of hypothyroidism is neither applicable to the treatment of older patients with large nodular goitres, nor does it prevent the cumulative incidence which rises linearly with time after one year. There is a growing belief that ^{131}I is now the treatment of choice for thyrotoxicosis in children as well as in adults. The safety of radioiodine in the dosages used to treat thyrotoxicosis seems undisputed following the results of the cooperative thyrotoxicosis therapy follow-up study (Beierwaltes 1978, Saenger *et al.* 1968, Dobyns *et al.* 1974, Starr *et al.* 1964, Safa *et al.* 1975).

The reader is invited to draw his own conclusions regarding the value of low-dose ^{131}I treatment. Domestic arrangements and the population being treated will also dictate local policy. The present study is now complete and the policy at this centre since January 1979 has been to continue with the 2 mCi dose, but repeat doses are given after 6-monthly intervals instead of annually in the hope of retaining the advantages and increasing patient convenience.

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