RADIOIODINE (I-131) TREATMENT OF HYPERTHYROIDISM AND SUBSEQUENT HYPOTHYROIDISM

F X Sundram

SYNOPSIS

Radioiodine (1-131) has been used to treat hyperthyroidism for almost forty years. The major problem with this form of treatment is the definite incidence of hypothyroidism, which is early or late, and cumulative. An analysis of 417 previously treated patients is presented in this paper, showing a cumulative 6 year incidence of hypothyroidism of 12.9%. After 1-131 therapy there were no significant differences in the incidence of hypothyroidism related to age, sex, size of gland or nodularity of gland, or dose of radioiodine administered. The risks associated with the use of radioiodine are discussed. The trend towards the use of larger 1-131 doses overseas is noted, with patients subsequently maintained on Thyroxine. It is hoped that patients would be referred for radioiodine therapy without being started on antithyroid drugs.

INTRODUCTION

Prevalence of hyperthyroidism in the general population (in U.S. and U.K.) has been estimated to range from 0.2% to 2% (1). In Singapore, presently about 300 new cases are treated with 1-131, for hyperthyroidism per year. The true incidence, including those seeking treatment elsewhere or not treated at all is not known.

Antithyroid drugs have been used for almost 40 years and are the initial management for hyperthyroidism in most patients. Presently antithyroid drugs appear to produce permanent remissions in 20-30% of patients given this form of treatment for an appropriate period of time (2). Antithyroid drugs may decrease serum thyroid stimulating immunoglobulins (TSI), as hyperthyroid patients go into remission on antithyroid drugs (3). Failure of triodothyronine to suppress radioiodine uptake, which has been used to predict relapse after antithyroid drugs with moderate success (4, 5, 6) was found to correlate well with the presence of TSI. Recent reports (7) suggest that prognosis of recurrence or relapse after a short course of antithyroid drugs (say 6 months) is no worse, but more data needs to be acquired for confirmation. Side-effects of antithyroid drugs are relatively uncommon — allergic skin reactions and agranulocytosis (0.1%).

Surgical management (sub-total thyroidectomy) is effective in producing a permanent cure in up to 85% of patients treated surgically. The problems with surgery include a significant morbidity (0.5% damage to laryngeal nerve) and occasional mortality (0.1 to 0.5%) depending on the skill of the surgeon. The risks with surgery increase as thyroidectomy becomes a less common operation and the surgical skill decreases. The incidence of hypothyroidism following surgery is reportedly similar to that following radioiodine, i.e. a continued incidence of 2.3% a year (8)

Department of Nuclear Medicine
Singapore General Hospital
Outram Road
Singapore 0316

F X Sundram, MBB Ch, M Sc (Nucl Med),
Consultant

PATIENTS AND METHODS

An average number of 180 patients per year was treated for thyrotoxicosis with radioiodine prior to 1981. A retrospective study was done of patients who had had radioiodine (I-131) therapy for treatment of thyrotoxicosis, for the years 1973, 1974 and 1975 and who maintained their follow-up appointments up to the end of 1980, to determine incidence of hypothyroidism. The study could indicate how treatment policies affected the onset and incidence of hypothyroidism.

Patients were classified according to age, sex, size of thyroid gland, nodular or smooth gland, dose of I-131 administered, measured I-131 uptakes and biochemistry (serum thyroxine (T4) levels). TSH levels were available routinely only from 1981.

A total of 417 patients who had I-131 therapy was available for evaluation (100 male and 317 female). Mean age at time of first I-131 treatment was 52 years for both men and women (range 25-91 years). In principle iodine-131 treatment for hyperthyroidism was usually avoided in patients under 40 years of age, unless surgery or antithyroid drugs was contraindicated, or was refused by the patient.

The doses of I-131 prescribed to the patient were empirical and ranged from 3—20 mCi (average 6.7 mCi). Higher doses were given to patients with nodular goitres, and lower doses for those with diffuse goitres. Likewise those with low uptake in their thyroid glands (as determined from diagnostic doses of I-131) were given higher doses as compared to those with good uptakes. Similarly those patients with larger glands (estimated by palpation and compared to size of normal gland) were given larger treatment doses of radioiodine compared to those with smaller thyroid glands.

After treatment with radioiodine, patients were seen regularly at 3—4 month intervals for the first year and subsequently at 6—12 month intervals. Follow up continued until December 1980 or death of patient. Hypothyroidism was diagnosed on clinical findings, and thyroxine levels in serum. Replacement therapy was avoided for the first 4—6 months after I-131 treatment if the clinical situation permitted.

RESULTS

100 males and 317 female patients who received radioiodine therapy were available for assessment. 4% of patients were hypothyroid 1 year after I-131 therapy while after 6 years the cumulative incidence is 12.9%, or an average rise of 2.2% per year.

Then men had an incidence of 9% becoming hypothyroid as opposed to 14.1% for women. A total of 54 out of 417 patients became hypothyroid during the six-year follow up period giving a cumulative incidence of 12.9%. Nine were male (9%) and forty-five were female (14.1%).

Table 1 shows relation of dose of I-131 to those becoming hypothyroid. It is noted that since the dose of radioiodine was tailored to the size and nodularity of gland there is no significant difference in the incidence of hypothyroidism with the larger doses. This is also borne out in Table 2 which relates the 24 hour dose in thyroid as calculated from uptake studies to the number of patients becoming hypothyroid.

46 patients needed a second dose of radioiodine (11% of patients) and of these 7 or 15.2% became hypothyroid (Table 3). The second or subsequent dose of I-131 was generally the same as the first dose. The average serum thyroxine (T4) of all the patients was 12.7, while the average T4 of those who became hypothyroid was 13.2,

Table 4 shows incidence of hypothyroidism in relation to gland size. It would appear that a larger number of patients with normal-sized or moderately enlarged glands became hypothyroid, but this is not statistically significant.

Table 5 shows that of 54 patients becoming hypothyroid thirty seven (68.5%) had smooth glands and seventeen had nodular glansds (31.5%). This is probably related to the more uniform uptake of I-131 in diffuse glands. There is no significant difference however in the average number of months before diffuse glands became hypothyroid as compared to the nodular glands, though it would seem that the diffuse glands became hypothyroid earlier after I-131 treatment.

Table 1
Patients distributed according to total dose of I-131 administered

Total Dose (mCi of I-131)	No. of patients	No. Hypothyroid	Hypothyroid
	1	0	0
4 — 5.9	127	19	14.9
6 — 7.9	177	21	11.8
8 — 10.0	67	8	11.9
10	45	6	13.3
	417	54	12.9

Average Dose = 6.7 mCi

Table 2
24 Hours dose calculated from diagnostic uptake

Dose administered	6.7 mCi (average) Range 3 — 20 mCi		
24 Hr dose (mCi)	4.9 mCi (average) range 0.8 — 16 mCi		
	No. treated	No. Hypothyroid	%
0 — 3.9	136	17	12.5
4 — 5.9	192	26	13.5
6 — 7.9	68	8	11.7
8 — 9.9	12	2	16.7
10	9	1	11.0
	417	54	12.9

Table 3: Subsequent Doses

Total Number of Patients = 417 Total Number of Hypothyroid = 54
No. of patients needing 2nd dose = 46 No. of Hypothyroid = % = 15.2
No. of patients needing 3rd dose = 3 No. Hypothyroid = 0 % = —
No. of patients needing more than 3 doses = Nil

Table 4: Gland Size

	No. of patients	No. Hypothyroid	% Hypothyroid
Gland 1 × Normal	129	21	16.3
2 × Normal	159	19	11.9
3 × Normal	81	10	12.3
4 × Normal	48	4	8.3

Table 5: Hypothyroidism in relation to gland nodulrity and time of onset

Total No. of hypothyroid patients (54/417)	Smooth Gland (37/267)	Nodular Gland (17/150)
Average No. of months after Ist dose to become hypothyroid	22.3 months	27.3 months

DISCUSSION

Hypothyroidism

Radioiodine therapy for hyperthyroidism was well established by the early 1950's and it subsequently became apparent that hypothyroidism was a common sequelae. There was not only an early incidence of hypothyroidism of 26 — 43%, but studies also showed an annual increase in the onset of hypothyroidism (9).

Results from the present study indicate that there is a definte though low incidence of hypothyroidism following I-131 therapy — 4% in first year and rising to about 13% at the end of the 6th year, giving a cumulative incidence of about 2.2% annually. Other studies have a somewhat higher early incidence of hypothyroidism and a cumulative increase of 3% yearly (10, 9). This is probably partly due to the generally higher doses of I-131 used abroad compared to the lower doses used in Singapore. It may also reflect a difference in our own patient population, as Blacks in the U.S. appear less likely to become hypothyroid. The lower incidence of hypothyroidism may also be due to increased resistance to radioiodine effects, resulting from the ingestion of antithyroid drugs, since many of our patients had failed medical treatment. Nevertheless there is no significant difference in the present study in the incidence of hypothyroidism for the varying doses of I-131 administered to patients — this is explained by the empirical adjustment of dose to size of thyroid gland, the diagnostic uptakes and to nodularity of glands. Most of the patients had a 24 hour dose to the thyroid of between 4-8 mCi with the overall average dose being 4.9 mCi.

Incidence of hypothyroidism generally correlates with amount of radioiodine delivered to thyroid gland, and lower doses have been suggested in order to reduce the incidence of hypothyroidism (11, 12, 13). It appears however that the incidence of hypothyroidism long after low-dose therapy with I-131 is not different from that following conventional doses (14).

Hypothyroidism tends to occur more frequently in the first few years following radioiodine therapy and surgery. Though this would suggest that the initial early incidence is related to the I-131 dose, it has been suggested to the natural history of Graves' disease itself than to the modality of treatment, since it is seen after all forms of treatment (15).

It has been suggested that there is an increasing incidence in hypothyroidism following radioiodine (16) but this is probably due to subjective changes over the last thirty years as well as the earlier recognition of hypothyroidism following the introduction of TSH assays (17). Becker et al (2) in a follow-up study of 11,000 patients treated with radioiodine note that after a mean follow-up period of 7.5 years, 58.9% of the patients were euthyroid, 34.9% were hypothyroid and 6.3% had a recurrence. Comparing a group of 5,200 somewhat older surgically treated patients with follow-up of 12.7 years, 61.6% of this group were euthyroid, 24.8% were hypothyroid, and 13.6% had a recurrence. So there is a definite incidence of hypothyroidism following surgical treatment too.

Carcinogenesis and Leukemogenesis

Since radioiodine was introduced as treatment for hyperthyroidism about forty-years ago, there have been fears about radiation — induced cancer and leukemia. To date however, almost a million patients have been effectively treated with radioiodine, while publications worldwide up to 1981 contain only 26 cases of thyroid cancer (18). In a group of 8,000 hyperthyroid patients surgically treated, 32 unsuspected thyroid cancers were found (3.8 per thousand). In the same study, (19) in 16,000 patients treated with radioactive iodine, only 9 malignant neoplasms were found (0.56 per thousand) in an eight-year follow up. These and other studies (20), indicate that the risk of thyroid cancer following radioiodine appears to be insignificant. The explanation for this low risk, is interference with their response to TSH, following radioiodine treatment, or reduction in number of thyroid cells at risk.

The risk of leukemia has been studied (21, 22). Both these studies with very large numbers of patients did not find any excess of thyroid cancer, leukemia or cancer in general. Other investigators, similarly show no significant increase in incidence of leukemia in hyperthyroid patients treated with radioiodine (23, 24). It must be emphasised that patients treated with I-131 should have regular long-term follow-up.

Genetic and foetal risks

Ionising radiation can cause genetic disorders which could be transmitted to later generations by gene mutations or chromosomal aberrations. As such there is concern about gonadal radiation dose and foetal radiation. In most patients with hyperthyroidism given I-131 therapy, the gonadal radiation dose will be similar to that from an I.V.P. (intravenous pyelogram) or barium enema (25). No harmful effects on subsequent fertility and birth history of I-131 treated patients, or on health status or reproductive history of the progeny, have been shown following treatment for hyperthyroidism (26, 27, 28, 29) or for thyroid cancer (30), through the numbers of patients were small.

The genetic risks are of course not relevant if the patient does not father or conceive a child, and this is a valid consideration in the Singapore context of voluntary sterilisation. It is obviously important that patients who are pregnant or lactating do not receive radioiodine therapy, since the foetal risks are potentially serious, especially in the first three months of pregnancy. Pregnancy should be avoided for at least a year by women who have just been treated with radioiodine.

SUMMARY

In contrast to surgery and antithyroid drugs, radioiodine therapy is an inexpensive and effective means of curing patients with hyperthyroidism, though in the not too distant future treatment directed at the auto-immune process of Graves' Disease may be possible. Surgery may be advisable in patients with large goitres or rapidly progressive eye disease or if malignancy is suspected. The current approach is for aggressive treatment with radioiodine in the first place rather than a trial of antityhroid drugs (31); it is aggressive from the point of view of large radioiodine doses and also from the point of view of treatment at a younger age (8). To quote from a letter by Williams and Halnan (32) of the Administration of Radioactive Substances Advisory Committee (ARSAC) in the U.K.: "Age restrictions recommended in Britain for the past few decades should now be removed. Those treating thyrotoxicosis should now free to act on their clinical judgement regarding their choice of treatment, whatever the age of the patient."

AKNOWLEDGEMENT

The authors gratefully acknowledges the help of Miss Jenny Ng who typed the manuscript, and the assistance of Mr P Hoon and Mrs Lim C C. I also wish to thank Mrs Tang, who collated the data and Mr H J Toh, our Physicist who did the statistical analysis. I wish to record my appreciation to the following members of the Thyroid Work Group, whose patients were studied — D B C Tan, Dr V K Sethi, Prof J S Cheah, Prof P B B Yeo, Dr H M Gwee, Dr B Y Tan, Dr (Mrs) Y T Tan, Dr K Nadarajah, Dr H C Chan. I gratefully acknowledge the encouragement from dr S E Aw, Head, Nuclear Medicine Department.

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