LONG TERM FOLLOW UP OF PATIENTS TREATED FOR HYPERTHYROIDISM WITH LOW DOSE RADIOACTIVE IODINE

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INTRODUCTION

RADIOACTIVE iodine (iodine-131) has been used extensively during the past 30 years for the treatment of hyperthyroidism and has been shown to control this disorder in the majority of cases in which it has been used. There have been varying reports of the incidence of post-radiation hypothyroidism which has been reported to be as high as 70 per cent in patients followed up for 10 years (Beling and Einhorn, 1961; Dunn and Chapman, 1964; Nofal, Beierwaltes and Patno, 1966; Green and Wilson, 1969). In recent years smaller doses of iodine-131 have been used to try to minimise this complication (Smith and Wilson, 1967; Hagen, Ouellette and Chapman, 1967; Hagen, 1968; Smith, Munro and Wilson, 1970, Blahd and Hays, 1972; Rapoport, Caplan and De Groot, 1975).

The experience of this unit with conventional doses of iodine-131 (using approximately 150 μCi per gram thyroid tissue) has been reported (Bhatia, Hadden, Montgomery and Weaver, 1968). Since then we have prescribed lower doses of approximately 70 μCi per gram of thyroid tissue, and from 1970 doses of approximately 35 μCi per gram. We have used these two doses rather than a dose calculated from neck uptake data. Furthermore, these doses could be given to outpatients without the need for inpatient supervision and disposal of excretory products.

The purpose of this paper is to report our experience using these smaller doses of radioactive iodine in the management of patients with hyperthyroidism.

PATIENTS AND METHODS

Patients were referred to the Metabolic Unit of the Royal Victoria Hospital from all parts of Northern Ireland between 1968 and 1973. The diagnosis of hyperthyroidism was made on the clinical findings and the standard biochemical tests then available (protein bound iodine, T₃ red cell uptake and serum cholesterol). Iodine-131 neck uptake studies were often performed for diagnostic purposes prior to therapy. The size of the thyroid gland was estimated by palpation. Iodine-131 was not given to patients under 40 years of age.

Before 1964, doses of iodine-131 calculated to deliver 6000 to 8000 rads to the thyroid, or 150 μCi per gram of thyroid tissue were used in the Metabolic Unit (Bhatia et al, 1968). Doses in the region of 8.5 mCi were used until 1964 when the
dose routinely used was reduced to about 5 mCi. From 1968 a standard dose of 2.5 mCi was given routinely to those patients where radioactive iodine was indicated. In 1970 a smaller standard dose of 1.25 mCi was introduced. From 1968 propranolol, 160 mg per day in divided doses, was given until the iodine-131 had taken effect (Hadden, Montgomery, Shanks and Weaver, 1968). Although a random allocation to treatment with 2.5 or 1.25 mCi was not followed, we do not believe that there was any real clinical or biochemical difference between the two groups (Tables 1 and 2). One hundred and seventeen patients received 2.5 mCi

Table 1  
*Comparison of ages and thyroid size in two dosage groups*

| Dosage | Patients remaining euthyroid (at least 5 years) | Mean age (years) ± SD | Mean thyroid size (g) ± SD |
|--------|-----------------------------------------------|----------------------|--------------------------|
| 2.5 mCi doses | Patients remaining euthyroid | 52.3 ± 10.7 | 33 ± 10 |
|        | Patients now hypothyroid | 49.8 ± 8.7 | 30 ± 7 |
| 1.25 mCi doses | Patients remaining euthyroid (at least 5 years) | 51.3 ± 8.4 | 32 ± 10 |
|        | Patients now hypothyroid | 48.1 ± 10.3 | 35 ± 5 |

Table 2  
*Relative degree of thyroid overactivity at first treatment*

| Dosage  | Euthyroid (at least 5 years) | Now hypothyroid |
|---------|-----------------------------|------------------|
| 1.25 mCi doses | No. of patients | Mean PBI ± SD | No. of patients | Mean PBI ± SD |
| Single dose | 22 | 11.4 ± 2.4 | 2 | 11.8 ± 2.9 |
| 2 doses | 10 | 11.7 ± 2.1 | 2 | 11.4 ± 1.8 |
| 3 doses | 4 | 13.3 ± 2.2 | 1 | 10.0 |
| 2.5 mCi doses | Single dose | 24 | 11.7 ± 2.2 | 30 | 11.1 ± 2.5 |
| 2nd dose (1.25 mCi) | 1 | 14.8 | 2 | 13.0 |
| 2nd dose (2.5 mCi) | 8 | 9.9 ± 1.6 | 7 | 12.5 ± 0.9 |

iodine-131 and 77 of this group have been followed up for at least seven years. Seventy-one patients were treated with 1.25 mCi and 24 have been followed up for at least seven years. A number of patients treated with 2.5 mCi doses have been followed up for 10 years and a few of those treated with 1.25 mCi doses have been followed up for eight years, but the numbers become too small to make valid
comparisons. Patients remaining biochemically hyperthyroid after three to four months received a further dose of radioactive iodine and a number of patients required multiple doses (Tables 3 and 4).

Table 3

1.25 mCi doses (71 patients)

| Total dose (mCi) | No. of patients treated | Per cent |
|------------------|-------------------------|----------|
| Single dose 1.25 | 28                      | 39.4     |
| 2 doses 2.5      | 17                      | 23.9     |
| 3 doses 3.75     | 11                      | 15.5     |
| More than 3 doses | 15                    | 21.1     |
| (mean 7.4 ± 3.1) |                         |          |

Table 4

2.5 mCi doses (117 patients)

| Total dose (mCi) | No. of patients treated | Per cent |
|------------------|-------------------------|----------|
| Single dose 2.5  | 79                      | 67.5     |
| 2 doses 3.75     | 3                       | 2.6      |
| 2 doses 5.0      | 16                      | 13.7     |
| 3 doses 6.25     | 2                       | 1.7      |
| 3 doses 7.5      | 10                      | 8.5      |
| More than 3 doses | 7                      | 6.0      |
| (mean 12.1 ± 2.4)|                         |          |

![Graph showing cumulative incidence of hypothyroidism](image)

**Fig. 1** Cumulative incidence of hypothyroidism following 2.5 mCi and 1.25 mCi doses of iodine-131. Results of single and multiple doses shown separately.
The diagnosis of hypothyroidism was made on the clinical features together with a PBI of less than 3.5 μg/100 ml or T₃ red cell uptake of less than 10 per cent. In recent years serum T₄, T₃ and TSH values by radioimmunoassay have been in use and the diagnosis confirmed by low T₄ and T₃ levels with an elevated TSH. The cumulative incidence of hypothyroidism was calculated by the life-table method (Berkson and Gage, 1950; Cutler and Ederer, 1958) which provides a corrective factor for patients lost to follow up.

RESULTS

Figure 1 shows the results of the two dosage regimes. Because the number of patients followed up between eight and ten years are relatively small, a comparison of the incidence of hypothyroidism in the two groups has been made at seven years.

![Graph showing percentage of hypothyroid patients over years after 131I treatment]

Fig. 2 Comparison of results with 2.5 mCi and 1.25 mCi doses of iodine-131 with results of Bhatia et al (1968).

Our experience with higher doses of iodine-131 (Bhatia et al, 1968) up to six years is shown for comparison (Fig 2).
At seven years 38.4 per cent of patients treated with a single dose of 2.5 mCi were hypothyroid, and of those followed up for ten years, 51.3 per cent were hypothyroid. Patients receiving multiple doses of 2.5 mCi (mean dose 6.9 ± 2.9) showed a cumulative incidence of hypothyroidism of 36.4 per cent at seven years, which did not increase at ten years.

At seven years 11.7 per cent of patients treated with a single dose of 1.25 mCi were hypothyroid, and of those patients followed up to eight years no more became hypothyroid. Hypothyroidism occurred in 17.4 per cent of those receiving multiple doses of 1.25 mCi (means 4.5 ± 2.8) and there was no increase at eight years.

The mean duration of biochemical hyperthyroidism following first treatment was 6.8 ± 7.7 months in the 2.5 mCi dose group and 8.5 ± 8.8 months in the 1.25 mCi dose group. Thirteen patients treated with 2.5 mCi doses were lost to follow up before five years and two patients died of causes unrelated to their hyperthyroidism. Five patients treated with 1.25 mCi doses were lost to review before five years and five patients died.

Two patients treated initially with 1.25 mCi remain on long term antithyroid drug treatment with carbimazole. One case was resistant to multiple doses totalling 15.0 mCi while the other case, treated with two doses of 1.25 mCi is now euthyroid. There were four cases of late relapse of hyperthyroidism (after three years) in the 1.25 mCi group. These patients were treated with further doses of iodine-131. One patient first treated with a 2.5 mCi of iodine-131 remains on carbimazole following relapse of hyperthyroidism at five years and multiple doses totalling 12.5 mCi. There was one other late relapse at six years in the 2.5 mCi group.

At the most recent review no patient remained hyperthyroid.

DISCUSSION

There is great variability in the reported incident of post-radiation hyperthyroidism. The difficulties in analysing data which involves variations in length of follow up can be minimised by using the lifetable method. Glennon et al, 1972 have compared several previous studies using this method and their results are shown in Fig. 3.

Figures 1 and 2 show that the annual incidence of hypothyroidism can be substantially reduced by the use of lower doses of iodine-131. The difference in incidence of hypothyroidism between the two low dosage groups at seven years was significant (p<0.05), with the proviso that the statistics were done on retrospective data and the treatments were not strictly randomised. No statistics were possible on the data of Bhatia et al for comparison. The argument against low dose iodine-131 therapy is that patients may remain hyperthyroid longer until the iodine-131 has taken effect, and that the patients will be subjected to repeated treatments and frequent attendance at outpatient clinics. However, the mean period of biochemical hyperthyroidism did not differ greatly in the two dosage groups studied, although the number of retreatments was greater in the 1.25 mCi dose group.

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Individual sensitivity to radioiodine is a possible factor in the development of hypothyroidism. No difference in age or size of the thyroid was observed in those patients requiring multiple doses nor was there any apparent difference in the degree of thyroid overactivity at first treatment in patients requiring single or multiple doses, or in those becoming hypothyroid.

These findings differ from the recent reports from the USA of a six year incident of hypothyroidism of 10 to 25 per cent following doses of 3 to 4 mCi (Cevallos et al, 1974; Glennon et al, 1972). It may be that the natural history of hyperthyroidism differs in different communities and that autoimmunity may be a factor in the ultimate development of hypothyroidism in patients treated with iodine-131.

Our policy of restricting iodine-131 treatment to patients over the age of 40 years may have contributed to the apparent high incidence of hypothyroidism at review compared with the results of American workers. Green and Wilson (1964) reported a lower incident of hypothyroidism in patients under 40 years of age, but attributed this to a larger thyroid gland in those younger patients treated. Bhatia et al (1968) found a higher incidence of hypothyroidism in patients aged 40 to 49 years compared with patients over 60. No definite trend was observed in the present series.
We have shown a difference in the results of treatment with two low dose regimens and compared this with our previous experience of more conventional doses of iodine-131 in this community. The lower incident of permanent hypothyroidism is offset by the need for repeated treatments in the 1.25 mCi group. As our patients are kept under regular review, it may be better to accept a higher rate of hypothyroidism, as this can be easily treated, and avoid frequent retreatments. Accordingly, we continue to use 2.5 mCi as a routine dose and retain the lower dose for milder cases.

SUMMARY

The cumulative incidence of hypothyroidism after therapeutic radioiodine for hyperthyroidism in patients over 40 years was 38 per cent seven years after a single dose of 2.5 mCi iodine-131, and 12 per cent seven years after a single dose of 1.25 mCi.

Thirty-three per cent of patients treated with 2.5 mCi required further doses, compared to 60 per cent of patients treated with 1.25 mCi. Where close supervision and outpatient follow up can be attained, the use of low dose radioiodine therapy can result in a much lower incidence of post-radiation hypothyroidism.

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GASTROINTESTINAL ENDOSCOPY. AN INTRODUCTION FOR ASSISTANTS. D. Hollanders. (Pp 168; figs 49. £4.75). London: Bailliere Tindall, 1979. IT is now over forty years since Mr. Harold W. Rogers, assisted by Dr. Francis Avery Jones, passed the first semiflexible gastroscope at St. Bartholomew's Hospital. Today fibre-optic endoscopy plays a key role in the investigation and management of digestive disease.

The instrumentation is now widely available and if it is to continue to be widely available as resources contract emphasis must be placed on careful handling of the equipment by well-informed assistants and endoscopists.

There are now many texts dealing with the techniques and interpretation of gastrointestinal endoscopic procedures but few are of practical value to the nurse or radiographer designated to assist in their performance. This small text fills a gap in the British Literature by giving all of the necessary information with which an assistant should be familiar. Subjects such as physical principles, equipment design and medication for endoscopy are well presented without too much technical detail.

The most useful chapters deal with the assistant's role both in the care of the patient and in the care of the equipment. Since these instruments are both fragile and expensive care to detail in their cleaning and handling is essential if expensive repairs and shortened instrument life are to be avoided. This book should be available in endoscopy units as an introduction for the trainee endoscopist and trainee assistant alike.

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