

# Guidelines for the use of radioiodine in the management of hyperthyroidism: a summary

PREPARED BY THE RADIOIODINE AUDIT SUBCOMMITTEE OF THE ROYAL COLLEGE OF PHYSICIANS COMMITTEE ON DIABETES AND ENDOCRINOLOGY, AND THE RESEARCH UNIT OF THE ROYAL COLLEGE OF PHYSICIANS

**ABSTRACT**—Radioiodine ( $^{131}\text{I}$ ) therapy is indicated in patients with nearly all causes of hyperthyroidism. It may safely be given to patients of all age groups but is less often given to children under 10 years old. It is completely contraindicated in pregnancy and while breast feeding, but there is no increased risk of thyroid cancer, leukaemia or solid tumours. Administration of radioiodine must conform to regulations and definitions laid down by ARSAC and POPUMET. Medical staff authorising therapy must hold an ARSAC licence. The recommended strategy is to give an activity sufficient to render the patient rapidly euthyroid and maintain that state or achieve no more than a low rate of hypothyroidism in subsequent years. A range of activity (300–800 MBq) is suggested depending on the clinical state. Antithyroid drugs may be given before or after (or both) radioiodine if necessary. Full written information should be given to the patient and written consent obtained. A structured follow-up should be used ensuring regular measurement of TSH or FT4. Close cooperation with the patient's general practitioner is recommended throughout the assessment, treatment and follow-up. Shared care with a computer based follow-up system is recommended.

Radioiodine (iodine-131) has been used in therapy for hyperthyroidism for more than 50 years. It is indicated in cases of hyperthyroidism due to Graves' disease or toxic nodular goitre (solitary toxic adenomas or multinodular goitre) and is effective in curing hyperthyroidism in virtually all cases given single or multiple doses. Radioiodine is almost always not an appropriate treatment for thyrotoxicosis secondary to thyroiditis or for thyrotoxicosis associated with iodine excess. The total number of treatments in the UK is approximately 10,000 per annum.

Factors that influence the decision to proceed to radioiodine therapy include patient age, gender, diagnosis, severity of hyperthyroidism, the presence of other medical conditions, access to radioiodine, and patient and doctor preference.

Pregnancy represents an absolute contraindication

to radioiodine treatment. In female patients of reproductive age, their plans for pregnancy must be taken into consideration. Pregnancy should be avoided for 4 months after treatment owing to the risk of concentration of residual radioiodine in the fetus. If a patient is keen to achieve pregnancy, it may be necessary to postpone radioiodine treatment (and continue with medical treatment), even in relapsed disease, until breast feeding has ended.

Recent surveys of thyroid specialists have revealed marked differences in preference for antithyroid drug (ATD) therapy or radioiodine therapy in different parts of the world. However, there has been no large scale randomised trial comparing the three modes of treatment (ATD, surgery and radioiodine therapy) over the long term. In Europe, including the United Kingdom, radioiodine therapy is less readily considered the treatment of choice in young patients with Graves' hyperthyroidism than it is in the United States, though this situation is changing.

Radioiodine is most readily provided in clinics held jointly by endocrinologists and radiotherapists or specialists in nuclear medicine, or where the endocrinologist is licensed to administer radioiodine. Patients can be given clear advice regarding the time of therapy, omission of ATD, counselling regarding contraception, and follow-up arrangements.

Although thyroid cancer has been described in occasional patients treated with radioiodine, no relationship between radioiodine and thyroid cancer has been found in several large studies. There is, similarly, no evidence for an increase in leukaemia or solid tumours, with the possible exception of gastric cancer in one report. It should be noted that these studies included relatively small numbers of patients (<11,000) followed up for less than 40 years, determining that it is important to continue long-term follow-up of populations treated with radioiodine to ensure the accumulation of further evidence in support of its safety. Less direct information than for cancer risk is available regarding risks of congenital abnormality. There is no evidence of increased abnormality in small studies of the offspring of women treated with radioiodine. The risk in women and men has been estimated at 0.005%; not surprisingly, such a risk has not been identified in clinical studies.

As radioiodine therapy does not normally require

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the patient to be hospitalised, the cost is relatively low and comparable to that of ATD therapy; this is substantially less than the cost of surgical treatment which usually requires a stay of 3–5 days in hospital.

### Regulations for administration of radioiodine

- Those clinically managing thyrotoxic patients may request radioiodine therapy, but only medical staff who hold an appropriate Administration of Radioactive Substances Advisory Committee (ARSAC) certificate may authorise its administration.
- The Ionising Radiation Regulations (Protection of Persons Undergoing Medical Examination or Treatment) 1988 (POPUMET) indicate that the person clinically directing the exposure (ie the ARSAC certificate holder) is responsible for ensuring that everyone else complies with legislation, and that administration of radioactive substances is in accordance with accepted therapeutic practice.
- The person who administers the radioiodine to the patient is physically directing the treatment and must have been trained in the core of knowledge required by POPUMET.
- Both the ARSAC and the POPUMET regulations require a physicist to liaise with the certificate holder and ensure that radioactive substances are administered safely. This function is distinct from that of Radiation Protection Adviser (RPA) although it may be carried out by the same person.
- Radioactive iodine may be dispensed only in premises that have Her Majesty's Inspectorate of Pollution (HMIP) registration and authorisation in relation to the keeping and use of radioactive materials, and disposal thereof, in accordance with the Radioactive Substances Act 1993. If inpatients from another hospital are treated, notification of the administered activity should be sent to the RPA of the referring hospital; this is to ensure that each hospital remains within exemption limits or within any authorisation granted by HMIP.
- Local rules must be written that explain how the department will implement the Ionising Radiation Regulations 1985 and its approved code of practice.
- Administration of radioiodine must take place within a 'controlled area', the requirements of which are set out in the Ionising Radiation Regulations 1985 and Guidance Notes for the Protection of Persons against Ionising Radiation arising from Medical and Dental Use (1988).

### Clinical guidelines

#### *Strategy for administration*

The following criteria have been suggested at various times:

- An activity sufficient to render the patient rapidly euthyroid within 3–4 weeks and preferably to maintain that state or to limit the incidence of hypothyroidism in subsequent years to a low level.
- An activity large enough to render the patient rapidly hypothyroid within 3–4 weeks of therapy. In many centres there may be considerable variation in activity to achieve this outcome.
- Administration of very small activities of radioiodine together with an ATD.

The second of these strategies may be regarded as less than optimal since all patients will be required to take thyroxine replacement therapy. Administration of small activities usually results in inadequate treatment of the hyperthyroid state; this is undesirable, especially in the elderly, because of the adverse effects of excess thyroid hormones on the cardiovascular system.

There is no evidence that precision dosimetry leads to an improved clinical outcome.

*The recommendation is to administer enough radioiodine to achieve euthyroidism with the acceptance of a moderate rate of hypothyroidism, eg 15–20% at 2 years and 1–3% per annum thereafter. Although the ablative strategy may be more cost-effective than a 'middle of the road' approach, consideration should be given to the health gain value of remaining euthyroid.*

#### *Recommended activity*

It is clear that there are wide variations in current practice. The following activities are recommended as broad guidelines. It is considered essential to establish the aetiology of the hyperthyroidism using standard diagnostic tests and criteria before radioiodine is administered.

- 'Standard' case of hyperthyroidism (usually Graves' disease). First presentation, moderate (40–50 g) goitre, no significant eye signs. Guide activity: 400–550 MBq.
- Toxic multinodular goitre in older person. Mild heart failure, atrial fibrillation or other concomitant disease (eg cancer). Guide activity: at least 550 MBq.
- Toxic adenoma, usually mild hyperthyroidism. Guide activity: 300–500 MBq.
- Significant thyroid associated ophthalmopathy. Options in patients with eye disease are to postpone radioiodine treatment until eye problems have become stable, to proceed to radioiodine with careful monitoring of thyroid function to avoid periods of untreated thyroid dysfunction, or to administer glucocorticoid therapy at the same time as radioiodine and for a further 4–6 weeks, in view of limited evidence that steroids may have a protective effect. Radioiodine therapy may be contra-indicated if it is felt that it may cause deterioration in ophthalmopathy.

- Ablation therapy may be required for patients with severe accompanying medical conditions such as heart failure, atrial fibrillation or other concurrent medical disorders (eg psychosis). Guide activity for thyroid ablation, as an outpatient: 800 MBq.
- A further dose of radioiodine may be given 2 months or more after the first one.
- The maximum permitted activity for outpatient treatment is 800 MBq. Hospitalisation is necessary if a greater activity is used.

### *Pregnancy and breast feeding*

No patient in whom there is any chance of pregnancy may receive radioiodine therapy; if necessary, a pregnancy test should be performed. Women are advised not to become pregnant for 4 months after receiving radioiodine. If pregnancy occurs sooner than 4 months after treatment a termination is not mandatory but advice should be sought. There is no evidence of any fetal or maternal risk in pregnancy or its outcome in women who receive radioiodine *provided the above guidelines are followed*. A person living in the same house as a pregnant woman may receive radioiodine therapy provided there is no close or prolonged contact with the woman (Table 1). No patient may continue to breast feed once radioiodine has been administered to her.

### *Antithyroid drug administration*

ATD should be discontinued at least 2 days prior to radioiodine administration since their effect lasts for 24 hours or more. Where antithyroid medication is to be continued, it may be recommenced 3 days after radioiodine treatment without significantly affecting the delivered radiation dose. Compounds that contain iodine, such as amiodarone, may block iodine uptake for several months following cessation of therapy; iodine uptake measurements may be helpful in this instance in determining the activity required and the timing of radioiodine therapy.

### *Contraindications to radioiodine therapy*

- Pregnancy and breast feeding
- Situations where it is clear that the safety of other persons cannot be guaranteed
- There may be relative contraindications; for example, a person who is incontinent should have a urinary catheter
- Allergy to iodine; this is not normally a problem as the amount of iodine in radioiodine preparations is minute.

### **Assessing the patient for radioiodine therapy**

At the initial consultation, the clinician should record certain information:

**Table 1. Number of days for which patients should take special precautions, according to the activity of radioiodine administered**

| Precaution                                                                                                                                            | Administered activity (MBq) |     |     |     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-----|-----|-----|
|                                                                                                                                                       | 200                         | 400 | 600 | 800 |
| Avoid journeys on public transport                                                                                                                    | 0                           | 0   | 1   | 2   |
| Stay off work (even when it does not involve close contact with other people)                                                                         | 0                           | 0   | 1   | 2   |
| Avoid places of entertainment or close contact with other people                                                                                      | 1                           | 5   | 9   | 12  |
| Stay off work (when it involves close contact with other people)                                                                                      | 1                           | 5   | 9   | 12  |
| Avoid non-essential close personal contact with children and with pregnant women; work that involves close contact with children; radiosensitive work | 14                          | 21  | 24  | 27  |

- 1 For administered activities greater than 400 MBq (but not more than 800 MBq) the patient may travel home by private transport.
- 2 Total close contact time with any individual should not exceed 1 hour.

- *Clinical data* relevant to the prescription of radioiodine or to the outcome of treatment, with particular regard to: heart rate and rhythm; the presence of cardiac failure; concurrent cardio-respiratory disease; goitre size; goitre type (whether, as far as can be ascertained, diffuse or multinodular); the presence of eye signs; the most recent thyroid function tests.
- *Personal or social factors* that would determine the need for special advice concerning the administration of radioactive substances.

The person clinically directing radioiodine therapy or his/her deputy must always see the patient prior to radioiodine administration.

Where radioiodine administration takes place more than 7 days after the initial consultation, the person clinically directing therapy should see the patient again in order to be certain that the relevant clinical features (see above) have not changed. A deterioration in the patient's clinical state might place him/her at greater risk of developing thyroid storm or further exacerbation of hyperthyroidism following radioiodine treatment.

The person clinically directing the radioiodine treatment should ensure that a follow-up plan has been agreed to be undertaken either by the person

clinically directing the therapy or by the referring clinician.

### **Patient information and consent**

At the initial consultation the patient should be advised of treatment effectiveness, with particular regard to the slow onset of action of radioiodine, the probability of persistent/recurrent hyperthyroidism or of hypothyroidism, and the need for regular follow-up to detect hypothyroidism.

Before treatment, the patient should be advised of recommendations for protection from unnecessary radiation and informed of the implications of radioiodine treatment in relation to work, travel and contact with the family (Table 1). The patient is advised to remain away from work and to avoid prolonged close contact with children and with pregnant women for a period of time related to the activity of radioiodine received, and there may be similar restrictions on travel. A premenopausal woman must be informed about the rules concerning radioiodine therapy and pregnancy.

An information sheet should be given to patients following the initial consultation.

On the day of radioiodine administration, the patient should sign a consent form indicating that he/she understands the advice concerning radiation protection and (where appropriate) that she is neither pregnant nor breast feeding.

Following radioiodine administration, the patient should be given a coloured warning card clearly stating the date on which the radioiodine was taken, the total activity, and the duration for which special precautions are necessary; the card should be carried by the patient during this time. A telephone contact number should also be given on the card.

### **Management following radioiodine therapy**

In the first 2 weeks following administration of radioiodine the patient should be warned that he/she may experience palpitations or other exacerbations of thyrotoxic symptoms, especially if not euthyroid prior to treatment. This is particularly relevant in the elderly and patients with heart failure, for whom admission to hospital over the period of the therapy should be considered.

Prior to treatment the patient should be made aware of the importance of follow-up thyroid function tests. These may be carried out at the hospital where the radioiodine therapy has been administered, by the referring clinician or by the general practitioner.

If the patient is not receiving an ATD it is rare for hypothyroidism to develop within the 8 weeks following treatment; the first blood test should therefore be carried out after about 6 weeks. Levels of free hormone and thyroid stimulating hormone (TSH) should ideally be measured to determine accurately

the results of therapy. Persistent suppression of the TSH level may continue for several months. High levels of TSH suggest the development of hypothyroidism; this will be useful in determining the frequency of further follow-up. In patients who are biochemically euthyroid at 6–8 weeks a further set of thyroid function tests should be performed at 12 weeks after radioiodine therapy. In patients in whom large doses of radioiodine therapy are used, evidence of developing biochemical hypothyroidism may become apparent at this stage.

Patients should be warned to report recurrence of thyrotoxic symptoms or alternatively the development of symptoms of hypothyroidism. They should be advised to report sudden changes in symptoms as soon as they occur rather than wait for their planned appointment, as hypothyroidism may sometimes develop rapidly. In patients who remain hyperthyroid or become biochemically hyperthyroid following therapy, ATD treatment should be recommenced. These drugs should be gradually withdrawn 3–4 months after therapy to assess the late efficacy of radioiodine treatment.

If thyroid hormone levels remain elevated on withdrawal of antithyroid medication, repeat radioiodine therapy should be instituted. Patients who remain euthyroid following therapy should continue to be followed up, at lengthening intervals, and again should be warned to report sudden alterations in symptoms. Patients who become hypothyroid in the first 6–12 weeks following radioiodine treatment should be monitored carefully to ensure that it is not a transient phenomenon. Continuing rise in TSH levels with concomitant fall in free thyroxine levels suggests developing thyroid failure in these patients, so thyroxine replacement therapy should be commenced, increasing incrementally to an adequate replacement dose.

Patients who required digoxin prior to radioiodine therapy, for management of atrial fibrillation, should have an ECG performed when biochemically euthyroid, as sinus rhythm is frequently restored and digoxin may then be discontinued.

Patients should be reminded to avoid pregnancy for 4 months following radioiodine therapy, and contraceptive advice should be explicitly given if necessary.

### **Monitoring and follow-up**

Regular monitoring, in general practice, of patients who have undergone radioiodine treatment for hyperthyroidism is essential for the timely detection of developing complications. To aid this process it is recommended that a computer based purpose-designed form be completed at the time of treatment. This should record essential details and serve as a reliable method of patient identification. The prevalence of hypothyroidism in post-treatment patients has

been estimated as 24–90% over the patient's lifetime. However, unnecessary review of low-risk patients, at a specialist level, is a waste of resources and causes inconvenience and expense to the patient.

It is recommended that a fail-safe system be adopted that supports regular patient monitoring with standardised follow-up intervals and, possibly, investigation protocols. The extremes of unnecessary follow-up and of patients 'dropping through the net' will thus be avoided. Such a system will also provide information for the assessment and maintenance of the quality of care. The responsibility for life-long follow-up should not rest solely with the general practitioner; the patient has an important role to play, and the specialist has a legitimate interest in long-term follow-up. Shared care is a management strategy that facilitates joint responsibility in cost-effective follow-up.

#### *Communication between specialist, GP and patient*

After leaving the clinic, patients may think of questions that they would have liked to ask. In these circumstances it is not uncommon for the patient to seek further advice from the general practitioner who should be aware of the proposed treatment and should be told what advice to give the patient. This should be done within 1 week of the patient's visit to the clinic at which the decision was taken.

Following the administration of radioiodine, a standard letter indicating the activity given and the form of treatment should be received by the general practitioner within 1 week.

The letter from the specialist to the general practitioner should include a management plan outlining the clinical and biochemical data that should be determined and the intervals for reviews.

The cooperation of general practitioners in helping to trace non-attenders should be obtained. The role of patients in being responsible for their own well-being should not be overlooked; support and advice may be needed to ensure this involvement.

Patients requiring long-term follow-up should be aware of the need for regular review of their condition. They should be provided with an information sheet indicating the frequency of review appropriate to their condition, and the appropriate content of such a review.

#### *Follow-up intervals*

Follow-up intervals of 6–12 months are recommended, depending on clinical state. Longer intervals are recommended only for stable patients, supported by a fail-safe follow-up system. Intervals of 6–12 months are fairly arbitrary but systematic collection of follow-up data will provide the basis on which to review the recommendations.

#### *Recommended investigations*

T4 or FT4 measurements may offer the cheapest and most cost-effective approach in all post-treatment patients; they may not be as sensitive as TSH measurements but may be a useful indicator to investigate further. If TSH levels are high, consider more frequent review; if low, consider less frequent review.

#### *Monitoring methods*

Computerised clinical systems have been claimed to improve records and communication, provide useful clinical and administrative information, create organisational structure, assist quality assurance and support long-term follow-up. Such systems have been used for a number of years in the care of radioiodine treated patients and have provided the basis for the development of shared care. Shared care for other chronic disease has been shown to be cost-effective in a rigorous evaluation; it operates in several centres in the UK. The advantages of shared care for thyroid disease are reduced loss to follow-up, improved adherence to therapy, improved detection of hypothyroidism, cost-effectiveness compared with alternative methods of follow-up, and increased opportunity for audit and evaluation of care. The way forward is a unified approach with linked general practice and specialist records and a greater role for patients in their own care. A manual system could be used if a computerised system is not currently considered feasible, but both should have similar characteristics.

There should be an effective audit procedure to ensure quality of both information and the follow-up care provided by the system used.

#### **Conclusions**

Radioiodine therapy is safe and effective for most causes of hyperthyroidism. It is essential to adhere to the current regulation for administration of radioiodine in order to protect the environment as well as health care workers and other contact persons from radiation. Following therapy, adequate arrangements must be made for continuing follow-up and assessment. Initially this may be performed in hospital but usually after 1 year a dedicated follow-up system is recommended. Cooperation with the patient's general practitioner is essential at all stages of therapy and long-term follow-up. Regular audit of treatment and monitoring procedures is suggested.

#### **Members of the Radioiodine Audit Subcommittee**

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### Further reading

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## NEW TITLE

### Guidelines for the use of radio-iodine in the management of hyperthyroidism

Copies of the full guidelines can be obtained by sending a cheque for £7.50 (overseas price £11.00) to: The Publications Department, The Royal College of Physicians, 11 St Andrews Place, London NW1 4LE.