

SPECIAL COMMUNICATION

Radioiodine I-131 For The Therapy Of Graves' Disease

Malik Mumtaz¹, Lim Shueh Lin², Khaw Chong Hui², Amir Sharifuddin Mohd Khir³

¹ Island Hospital, 308 Macalister Road, 10450 Penang, Malaysia

² Department of Medicine, Penang Hospital, Jalan Resideni, Georgetown, 10990 Penang, Malaysia

³ Department of Medicine, Penang Medical College, 4 Jalan Sepoy Lines, 10450 Penang, Malaysia

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Abstract

Graves' disease is a common cause of hyperthyroidism. Treatment options for Graves' disease include antithyroid medication, surgery or radioactive iodine (I-131) or RAI. This review will focus on the approach to RAI therapy; discussing dose selection, patient preparation, and consideration before and after administering RAI, examining aspects of pre-treatment with antithyroid medication as well as discussing possible adverse events including hypothyroidism and possible worsening of thyroid-associated ophthalmopathy. Follow-up is lifelong with the aim of ensuring the patient remains euthyroid or on replacement therapy if there is evidence of hypothyroidism. While there are controversies in treatment of thyrotoxicosis with RAI, with appropriate patient selection and regular follow-up, radioiodine is a safe and effective modality in achieving high cure rates.

Keywords: radioactive iodine, Graves' disease, thyroid, treatment, medical sciences

Introduction

Radioactive iodine (I-131) or RAI as it shall now be referred to, has been commonly used for the treatment of both benign and malignant thyroid conditions since the 1940s. The aim of therapy is to treat hyperthyroidism by destroying sufficient thyroid tissue to render the patient either euthyroid or hypothyroid. Iodine-131 is a beta-emitting radionuclide with a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, and a range in tissue of 0.8 mm. It remains the radionuclide of choice for therapy because of its long half-life of just over 8 days.

The mechanism of action of RAI is physiological. Iodine is the precursor of thyroxine. The radioactive form of iodine is taken up by iodide transporter of the thyroid the same way as natural iodine and is similarly processed. The β particle destroys the follicular cell, gradually leading to volume reduction and control of the thyrotoxicosis. The indications and contraindications for RAI therapy are shown in Table 1.

Graves' disease (GD) is an autoimmune condition characterised by elevated levels of thyroid stimulating (TSH) receptor antibodies with

increased production of thyroid hormone. Among patients with hyperthyroidism, 60–80% have GD. It is 5–10 times more common in women than in men or children and is associated with a firm diffuse goitre, as well as clinically evident ophthalmopathy in 50% (1). Various important issues in therapeutic use of RAI are discussed in this review. Treatment options for GD include antithyroid medication,

Table 1 : Indications and contraindications for RAI therapy

The main indications for RAI therapy include the following conditions

1. Hyperthyroidism due to:
 - a. Grave's disease
 - b. Toxic multinodular goitre or
 - c. Hyperfunctioning thyroid nodules
 2. Non-toxic multinodular goitre
 3. Thyroid cancer.
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Contra-indications for RAI therapy

1. Pregnancy
 2. Breast feeding
 3. Severe uncontrolled thyrotoxicosis
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surgery and RAI therapy. The choice of treatment may differ from country to country but generally very few patients with uncomplicated GD are treated surgically (2).

Approach to RAI therapy

1. Selecting the appropriate dose of RAI

RAI is the most widely used treatment for patients with GD in the United States (2). Although therapy is well established for definitive treatment of GD, the approach to dosing remains controversial. This is due to differing goals of treatment (control of hyperthyroidism vs. avoidance of hypothyroidism).

Various techniques have been used to deliver adequate doses of radiation to the thyroid gland. These include calculations based on ultrasound determination of the volume of the gland and iodine uptake (3–5). Some authors advocate high doses of I-131 to render the gland hypothyroid in view of the complications that may occur with longstanding disease (6,7). This kind of approach is complex and increases hospital visits prior to therapy (8). The other is a fixed dose approach (2).

There is little evidence that using a calculated dose has any advantage over a fixed dose regimen in terms of preventing hypothyroidism (9,10). It is clear that no matter what the method used to determine the dose of therapy, most patients will ultimately become hypothyroid after RAI (11-13). A fixed dose regime is more convenient to use.

What is the optimal dose of RAI?

In a study comparing treatment with two single fixed first doses of RAI (14) of 185 MBq and 370 MBq, cure after RAI (defined by either euthyroid of all medications or biochemical hypothyroidism on a thyroxine replacement), was achieved in 85% of patients who received 370 MBq and 70% in the lower dose group. In addition, the second dose was administered to 30% of the lower dose group compared to only 15% of the higher dose group. The incidence of hypothyroidism at 1 year was 71.4% in the high dose group and 66.4% in the low dose group who required a second dose of RAI. The advantages of lower hypothyroid rates were lost if a second dose was administered. The authors concluded that a single fixed dose of 370 MBq is highly effective. Similar findings were noted from a study of 605 patients who were given various doses of RAI (15). Eighty-seven percent of those who were given 370 MBq were either hypo- or euthyroid.

Other authors argue that a larger fixed dose will minimise the need for re-treatment, and the morbidity and costs of the ineffective primary treatment. This approach uses high doses of RAI to deliver a dose of approximately 8 MCI (296 MBq)

to the thyroid at 24 hours. This requires a dose of 15 MCI (555 MBq) to be given (16). Cure rates were 86% at 1 year. Similarly, Kendal-Taylor et al. (17) used 555 MBq as a fixed dose and demonstrated that 64% of their patients were hypothyroid and 30% were euthyroid 1 year after therapy.

2. Considerations before RAI therapy

Patient preparation ensures efficacy of RAI and reduces the potential complications. Important issues like the consent procedure, pregnancy issues and timing of stopping medication, restarting therapy and possible complications of therapy should be discussed with the patient (18) and are summarised in Table 2. Certain medications and other substances such as radiographic contrast materials can interfere with RAI uptake and should be stopped before treatment. These are highlighted in Table 3. Some of these issues include:

Iodine restriction

All patients must discontinue use of all iodine containing medications and must be placed on an iodine-restricted diet to ensure adequate RAI uptake. While the timing of dietary restrictions is unclear for benign thyroid disease, recommendations for thyroid cancer patients may be as long as 10–14 days.

Antithyroid medication

Carbimazole (CMZ), Methimazole (MTZ) and propylthiouracil (PTU) are used for the primary treatment of thyrotoxicosis due to GD or as a means of preparing the patient for definitive therapy with surgery or RAI (19). Pre-treatment of selected patients is indicated in older patients, in those with severe hyperthyroidism and cardiovascular complications. In such patients it is common practice to achieve euthyroidism to reduce the risk of worsening of thyrotoxicosis due to radiation induced leakage of stored thyroid hormone, which can occur soon after RAI therapy (20).

Worsening of the thyroid function has been described in approximately 10% of patients given RAI and 0.3% may experience a thyroid storm whether they are pre-treated or not. While there may be a transient rise in hormone levels in all patients, in pre-treated patients, this increase does not lead to an exacerbation due to lower baseline thyroid function (21). Adjunctive antithyroid drugs reduce the biochemical exacerbation of hyperthyroidism directly after radioiodine treatment. Patients who are at lower risk may be treated with only beta-blockers, with significant improvement of symptoms particularly if the RAI can be given without too much delay.

Table 2: Important practical issues prior to administration of RAI Adapted from The Society of Nuclear Medicine Guidelines (18)

	Informed consent must be obtained after adequate discussion of the issues outlined below
Adequate explanation: Written information should be provided to the patient	<ol style="list-style-type: none"> 1. Pre-treatment issues 2. Fasting prior to therapy 3. How the iodine will be administered (liquid vs. capsules) 4. Possible complications and side effects 5. Alternative treatment options: antithyroid medication and surgery 6. Expected outcome to the patient: aims of therapy 7. The risk of hypothyroidism and lifelong L-thyroxine replacement 8. In women: Issues about delaying pregnancy for 4-6 months after the last dose of iodine In men: avoid fathering a child for a similar period of time 9. The necessity of lifelong follow up must be made clear
Written notification	<ol style="list-style-type: none"> 1. Date of stopping antithyroid medication 2. Date of resuming antithyroid medication 3. Date and time of therapy 4. Date of follow up visit
Radiation protection issues	<ol style="list-style-type: none"> 1. Patients must adhere to instructions 2. Precautions to avoid unnecessary exposure to family and co-workers, children and pregnant women 3. Mandatory urine pregnancy test performed <72 hours prior to RAI therapy

Table 3: Medications and other substances such as radiographic contrast materials that can interfere with RAI uptake and should be stopped before treatment

Type of medication or Substance	Duration of stopping treatment before RAI
Antithyroid medication (e.g., propylthiouracil, methimazole, carbimazole) and multivitamins	1-2 weeks for antithyroid drugs. Note: Beta Blockers can be continued 7 d for multivitamins
Expectorants, agar, Lugol's iodine, potassium iodide ("SSKI")	2-3 weeks, depending on iodide content
Radiographic contrast agents Intravenous (water soluble)	3-4 weeks (assuming normal renal function)
Amiodarone	3-6 monts or longer

Adapted from:

The Society of nuclear Medicine Guidelines (18), Martin A Walter, Matthias Briel, et al. BMJ 2007(26);334;514

Carbimazole and Propylthiouracil

PTU appears to be radioprotective. This effect persists for at least 7 days and for up to 55 days (22). The evidence suggests a reduced efficacy of RAI when patients are pre-treated with PTU (22,23). Unless the drug can be withdrawn for up to 2 weeks prior to therapy, it may be necessary to use a larger dose of RAI to overcome this problem. A dose of up to 555 MBq may be required (24). CMZ however does not appear to have this effect on efficacy of RAI therapy (22,25) as long as the treatment is stopped from 3–5 days prior to therapy (18). A recent meta-analysis suggests that all antithyroid medication should be withheld for at least a week prior to therapy (26). MTZ should be stopped a few days before therapy to improve the outcome (27). Based on the evidence it is compelling to stop PTU for up to 2 weeks prior to therapy and CMZ or MMZ for a few days but preferably 1 week prior to RAI.

Resuming antithyroid medication after RAI therapy

Resuming antithyroid therapy is not associated with an increased risk of recurrence of the hyperthyroid state or progression to hypothyroidism (28) unless given within a week before or after radioiodine where there is an increased failure rate of therapy and reduced the hypothyroidism rates respectively (26). MTZ restarted on the seventh day after RAI had no impact on thyroid function. There was however a difference in the final thyroid gland volume reduction at 12 months, 36% vs. 47%.

Lithium carbonate

Lithium is highly concentrated in the thyroid gland against a concentration gradient, probably by active transport. It induces a marked decrease in the release of preformed thyroid hormone from the thyroid. In higher doses it can also inhibit organic binding reactions (29). The use of lithium carbonate as an adjunctive therapy has been shown to be effective by some authors (30). The effect of lithium is to delay the release of the RAI from the thyroid, thus potentiating its therapeutic effects. Other authors have shown prospectively that lithium use for 3 weeks from the time of RAI compared to a control group without lithium therapy had little effect on cure rate (31).

3. Adverse events of therapy

While it is generally safe to give RAI, patients may experience some side effects of therapy. The risk of eventual hypothyroidism is high, especially after treatment of GD. There can be transient exacerbation of hyperthyroid symptoms due to

radiation thyroiditis. Perhaps the most worrying and potentially troublesome is potential worsening of thyroid associated ophthalmopathy (TAO) (18).

Thyroid Associated Ophthalmopathy

The definition of TAO may vary. Bartley et al. (32) provide the most acceptable definition. Patients with TAO may require specialist assessment (33) to determine the degree of severity, particularly when the prevalence of TAO in a local population was found to be 34.7%, with smokers 2.8 times more likely to have TAO than non-smokers (34,35). The natural history of TAO in GD is somewhat unclear. It may develop before, with or even after the onset of hyperthyroidism (36). It is generally accepted that treatment of thyrotoxicosis with antithyroid drugs does not affect the course of TAO (37) and neither does near-total thyroidectomy (38).

Progression of Thyroid Associated Ophthalmopathy (TAO)

One of the more controversial aspects of RAI therapy is whether RAI has any significant impact on TAO. The evidence is conflicting, perhaps related to the early study designs and retrospective nature of these studies. Various non-randomised studies that show exacerbation of TAO following RAI have been quoted; worsening is seen in as few as 3% of patients and as many as 53%. Bonnema et al. (24) discuss various non-randomised studies. The results on randomised studies on this issue are more consistent. These show a worsening of TAO in a proportion of patients. Tallstedt et al. (39) reported similar incidences of progression of TAO after antithyroid therapy (10%) and surgery (16%) but significantly higher rate after RAI (33%).

Bartelena and co-workers were able to prospectively demonstrate that while a number of patients have transient TAO after RAI, 5% have permanent TAO, which required treatment. This is not seen with MTZ therapy or in the group patients who received I-131 and prednisone (40). The patients in this study had mild ophthalmopathy (proptosis < 22 mm, intermittent diplopia or none, mild conjunctival or periorbital inflammation). The steroid treatment regime used oral prednisone at 0.4–0.5 mg/kg given daily, starting 2–3 days after RAI therapy and continued for 1 month. The dose of prednisone was then gradually reduced over the subsequent 2 months and stopped.

In another study (41), patients with minimally active TAO were treated with 405 ± 12.9 MBq of RAI. Antithyroid medications were withdrawn prior to therapy. Thyroxine replacement was commenced 2 weeks after I-131. The authors concluded that progression of TAO was not seen following RAI due

to early treatment to prevent hypothyroidism.

Hypothyroidism

The issue of risk of developing hypothyroidism has also been discussed earlier under the heading of the optimal dose of therapy. Hypothyroidism rates within the first year are very much dependent on the dose of RAI. The incidence of hypothyroidism after the first year is 2 to 3 percent per year. Hypothyroidism within the first year may be transient. In a study of 260 patients who received radioiodine therapy for GD, 67 developed hypothyroidism within 12 months. The hypothyroidism was transient in 58%. However, 70% of those with transient hypothyroidism became permanently hypothyroid in the subsequent 2 to 11 years (42).

4. Other Issues

RAI and pregnancy

The foetal thyroid at 10–12 weeks of gestation is capable of forming colloid, concentrating iodine, and synthesising thyroid hormones (43). RAI treatment is absolutely contraindicated in pregnancy, because it is readily transferred across the placenta. The damage to the foetal thyroid gland results in hypothyroidism and irreversible mental retardation (44,45). Despite the recommendations for routine pregnancy testing prior to RAI therapy (18,46), pregnant patients are inadvertently given RAI. There are reports of administration of RAI in early pregnancy (45). Radiation exposure in utero is determined by the gestational age, foetal thyroid activity and maternal thyroid uptake (47). Administration of a maximum dose of 15 mCi (550MBq) given up to 10 weeks of gestation does not severely affect foetal thyroid function and the low fetal exposure does not justify termination (48). There is no increase in birth defects or childhood malignancy in children born to mothers who had received radioactive iodine before the 10th week of gestation (49).

Limited evidence suggests that RAI given after 10–12 weeks results in neonatal hypothyroidism or cretinism. Termination of pregnancy may be advocated but dosimetry studies should be performed. If pregnancy is to follow to term, early screening for hypothyroidism is recommended (50).

Cardiovascular outcomes following RAI

A recent study (51) showed that chronic hyperthyroidism and not the treatment modality, is a cause of excess cardiovascular (CV) mortality. This can be attributed to cerebrovascular disease and atrial fibrillation (AF). AF occurs in 5–15%

of patients with hyperthyroidism (52). In a large study extending over 40 years (53) most of the excess deaths, which occurred in the first year after treatment, were related to the hyperthyroidism. Other factors contributing to the excess deaths were CV disease and femoral fractures. Radioiodine could not be accountable for the excess morbidity and mortality.

Radioiodine and risk of malignancy

The link between external head and neck irradiation and increased rate of thyroid carcinomas dramatically shown by the Chernobyl disaster of 1986 (54,55), has naturally raised concerns of possible carcinogenic effects of RAI as a source of ionising radiation. Although there are case reports suggesting a link, large epidemiologic studies revealed no association between RAI for GD and subsequent development of thyroid carcinoma (56–58).

The Cooperative Thyrotoxicosis Follow-up Study did demonstrate an excess risk of death from thyroid carcinoma in patients with RAI treated toxic Multi-nodular goitre (MNG). This association raises the consideration of genetic predisposition of those with MNG to thyroid cancer as in those with familial PTC have increased familial incidence of thyroid nodules and MNG (59).

There is no evidence for increased mortality from any other forms of cancer (58,59), including leukaemia (60). A recent cohort study (51) showed increased mortality from cancer (RR1.29) after RAI for hyperthyroidism, with an increased risk of death in patients older than 60 years at treatment. Mortality rose with the amount of RAI given and in those with nodular thyroid disease. There was also a suggestion of increased upper GI cancer in elderly males, but this observation has not been confirmed by other studies.

5. Follow Up of Patients who have received RAI

The efficacy of treatment of hyperthyroidism is best assessed with a Free Thyroxine level (FT4). Serum TSH may remain suppressed for long periods of time, weeks to months even when the patient is clinically euthyroid (61,62). It is important to monitor the patient for evidence of treatment failure or progressive hypothyroidism. Serum TSH should be measured at 6 to 12 month intervals. The patient should be aware that follow up is lifelong. As longstanding hyperthyroidism is associated with AF and osteoporosis (53), clinicians should be vigilant during follow up visits.

Conclusion

Based on current evidence, a fixed dose of RAI is effective to achieve treatment goals. Patients should be on a reduced iodine diet and antithyroid medication should be stopped prior to therapy and resumed one week after RAI if necessary. Patients with mild TAO may benefit from a course of prednisone to prevent worsening or progression of disease. Hypothyroidism need to be detected early and treated to prevent progression of TAO. There is little evidence to support increased risk of malignancy and worsening of CV disease following RAI therapy. Lifelong follow-up is important to ensure that recurrence of disease or hypothyroidism can be treated. In conclusion, RAI is a safe and effective modality for the treatment of GD.

Review criteria

Searching PubMed using the following search terms "Radioiodine for Graves' disease" and "I-131 therapy for thyrotoxicosis" performed a review of the literature". Abstracts and full-text papers published between 1990 and 2008 were the primary source of data. Some older abstracts from the 1960s and 1970s provided additional information.

Correspondence

Dr. Malik Mumtaz
MD (USM) FRCP (Edin) FRCP (Glasgow),
Fellowship in Nuclear Medicine (Glasgow), AM
Island Hospital, Penang
Email: mmumtaz66@gmail.com

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