Review Article

Radioactive iodine therapy in Graves' hyperthyroidism

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ABSTRACT

Graves' disease is a common condition encountered in clinical practice. The available modes of therapy for Graves' disease are antithyroid drugs, radioiodine and surgery. Radioiodine therapy is indicated in patients with nearly all causes of hyperthyroidism and is considered the treatment of choice for most patients with Graves' hyperthyroidism who are beyond the adolescent years. Pregnancy and breast-feeding are absolute contraindications. Although there are many ways of calculating the dose of radioiodine, fixed dose regimens are gaining acceptance. Hypothyroidism follows sooner or later in nearly all patients treated with radioiodine. Available evidence suggest that patients are best treated by a single thyroablative dose, the aim being elimination of hyperthyroidism, with larger doses accomplishing it with more certainty, and the inevitable hypothyroidism develops under physician control. Radioiodine therapy can lead to exacerbation of infiltrative ophthalmopathy and this can be prevented by the concomitant administration of corticosteroids. Radioiodine therapy for Graves' hyperthyroidism has no adverse effects on the health of the offspring of treated patients. There are no definitive data that provide evidence for increased rates of thyroid cancer, leukaemia, infertility or neonatal abnormality in patients treated with radioiodine. Radioiodine therapy is safe, definitive and cost-effective.

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INTRODUCTION

Graves' disease is a common endocrine disease. The essential goal in the management of thyrotoxicosis of Graves' disease is to reduce the hypersecretion of thyroid hormones. There are three forms of treatment—antithyroid drugs, radioactive iodine and surgery—each of which is not exclusive of the other. These therapeutic modalities have their own advantages, disadvantages, indications and contraindications.[1–3] The choice of therapy may be influenced by its cost, convenience, history of recent exposure to iodine, availability of skilled surgical expertise, local cultural factors, size of goitre, severity of disease, personal biases, as well as more objective data reflecting the risks and benefits of each of these.[4] The use of radioactive iodine therapy as the first line of treatment has gradually but steadily been increasing over the years and is presently considered to be the treatment of choice for most patients. We review the current role of radioactive iodine therapy in Graves' hyperthyroidism.

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HISTORICAL BACKGROUND

The idea of using radioiodine as a diagnostic and therapeutic tool was mooted by Karl Compton in 1936.[5] Robley Evans used a random beryllium mixture[6] to produce small quantities of ^{128}I for experimental work. Saul Hertz and Arthur Roberts were the first to use radioiodine ^{130}I for the treatment of hyperthyroidism on 31 March 1941.[7] In 1942, two groups of investigators published their preliminary results of radioiodine therapy in hyperthyroidism.[8,9] In 1946, the same groups published their results of radioiodine therapy in hyperthyroidism.[10,11] The use of ^{131}I became possible with the availability of the isotope from the Manhattan Project at Oak Ridge, Tennessee, USA.[12] From then on, only ^{131}I has been used for therapy. More than 50 years and thousands of patients later, it has not been possible to identify and individualize the dose of ^{131}I so as to achieve permanent euthyroidism.

MECHANISM OF ACTION OF RADIOIODINE

^{131}I emits both beta and gamma irradiation and is used universally for therapeutic purposes. It has a half-life of 8.2 days[13] and is administered orally as a capsule or in water. It is almost completely absorbed and is cleared from the circulation by thyroid epithelial cells and incorporated into the thyroid follicle where it remains for some finite period of time while undergoing radioactive decay. The effective half-life ($T_{1/2}$) in the thyroid is 866 hours.[14] Ninety-four per cent of the radiation dose in case of ^{131}I is due to particulate radiation and non-uniformity for ^{131}I is modest compared to other isotopes of iodine. The size of a thyroid follicle averages 0.2 mm and the path length of beta particles is 1 to 2 mm. Therefore, thyroid cells are irradiated even if they do not trap the radioiodine.

The most important damage caused by ^{131}I is to the genetic apparatus of the nucleus leading to structural alterations in the DNA and chromosomes. It produces single-strand breaks and base alterations in DNA. These damages are brought about by (i) the direct effect of ionizing radiation and (ii) free radicals generated by ionizing radiation. Acute radiation thyroiditis occurs within 2 weeks of exposure to ^{131}I, characterized by inflammation and eventual necrosis of some or all cells in the thyroid. Over time, there is atrophy and fibrosis.

RADIOIODINE THERAPY

Indications

For Graves' hyperthyroidism, ^{131}I therapy is often considered to be the treatment of choice. However, it is also used as therapy after antithyroid drug therapy has failed to achieve remission or for post-thyroidectomy recurrence of thyrotoxicosis. The selection of radioiodine as the first or second line of therapy depends on factors such as age of the patient, availability of isotope facilities, availability of surgical expertise and the

choice of the treating physician. Earlier, radioiodine therapy used to be reserved for older patients while children were given prolonged courses of antithyroid drug therapy. This scenario is changing.

Contraindications

As the isotope readily crosses the placenta, pregnancy and breast-feeding are absolute contraindications for radioiodine therapy. The foetal thyroid can concentrate iodine from the tenth week and administration of radioiodine results in foetal hypothyroidism and its attendant complications. The passage of radioiodine through breast milk can persist for up to 8 to 10 weeks after treatment.

It is necessary to rule out pregnancy before administration of radioiodine and it is also advisable that pregnancy should be avoided for four months after receiving radioiodine therapy.

Other contraindications include a history of hypersensitivity to iodine-containing compounds. Since the molar quantity of iodine is very low, the chances of hypersensitivity reactions are small. In those with such a history, pre-treatment with antihistamines may help prevent hypersensitivity reactions.

Radioiodine therapy should be delayed for several weeks or months in patients who have had chronic exposure to inorganic or organic iodine-containing foods or medications. This is because a high level of circulating iodide will prevent uptake of the administered radioiodine by the thyroid gland.

Dose calculation

The goal of therapy for thyrotoxicosis is prompt, predictable elimination of the hypersecretory endocrine state with a single dose of radioiodine.[15] There are many methods of determining the dose of ^{131}I to be given:

1. Fixed-dose regimen: All patients are given the same dose of radioiodine, irrespective of the gland size or its uptake of radioiodine.
2. A specific amount of radioiodine per gram of thyroid gland is given.
3. A specific amount of radioiodine per gram of thyroid gland is given but the dose of radioiodine is corrected for the uptake.
4. A specific amount of radiation is delivered to the thyroid.

The most commonly used approach is to determine the dose from the size of the thyroid and percentage uptake of iodine, using the formula:

$$\text{Dose in } \mu\text{Ci} = \frac{\text{Weight of the gland (g)} \times \text{desired } \mu\text{Ci/g} \times 100}{\text{24-hour uptake}}$$

Factors such as thyroid size, avidity of the thyroid gland for iodine, turnover of radioiodine within the gland, $T_{1/2}$ and prior or planned antithyroid drug therapy must be considered for the calculation of the dose of radioiodine.[16] Larger doses would be required in case of low uptake, large goitre and severe thyrotoxicosis. The dose should be increased by 25% in patients treated with antithyroid drugs prior to or after radioiodine therapy.[17] Bockisch *et al.*[18] state that the outcome with different schemes of radioiodine dose estimations varies. The problem with small fixed doses is the need for re-treatment with multiple doses due to inadequate control in many patients. On the contrary, a large single dose would result in quick control but may also cause early hypothyroidism in many patients. Using a sliding scale according to goitre size (3–5 mCi for small glands; 7–12 mCi for moderate-sized glands; 20–30 mCi in severe disease) may achieve some degree of individualization with acceptable cure rates and sequelae.

Nordyke and Gilbert[19] analysed a series of 605 patients treated with radioiodine to find out the optimal dose to achieve cure. They grouped the patients by age, gender, race, thyroidal uptake, gland weight and amount of ^{131}I given. Patients received 3, 4, 5, 6, 8 and 10 mCi. They concluded that cure was directly related to the dose of ^{131}I administered and there was no significant relation between cure and age, gender and >30% radioiodine uptake. They also found that cure and gland weight had an inverse relationship. In the light of the above studies,[18,19] using a fixed dose of radioiodine according to the goitre size is most appropriate in managing patients in developing countries. The schedule that is commonly followed is: 5 mCi for small glands (up to 40 g), 7–10 mCi for moderate-sized glands (>40 g but <80 g) and 12–15 mCi for large glands (>80 g).

Catargi *et al.*[20] studied the efficacy of individualized dosimetry to calculate and deliver a pre-determined target dose. This study found that there existed correlation between the intended and delivered dose. However, this did not in a predictable manner alter the outcome. Therefore, we do not favour the use of detailed kinetic studies to calculate the radioiodine dose.

Irrespective of the method used to determine what dose of radioiodine should be prescribed, there is a trade-off. Higher doses cure hyperthyroidism with great regularity, but cause more hypothyroidism, whereas low-dose therapy would result in persistent hyperthyroidism in the majority of patients.

Use of antithyroid drugs

The use of adjunctive drug therapy started early in the radioiodine era, when exacerbation of hyperthyroidism was noted shortly after ^{131}I therapy.[21] This was attributed to radiation damage and follicular disruption releasing preformed hormones into the circulation. Antithyroid drugs (ATDs) would block the synthesis of T3 and T4 and hence deplete the thyroid of its hormonal stores to make ^{131}I therapy less risky. This was supported by Larson[22] who estimated the T4 content in normal subjects and in patients with Graves' disease treated with propranalol or ATD and found the mean values to be 254, 295 and 115 μg/g, respectively. Even after 50 years of radioiodine use, the exact incidence of exacerbation of hyperthyroidism after ^{131}I therapy is not known; various series report a 0% to 3% incidence.[23] Burch *et al.*[24] studied the effect of treatment with ATD before radioiodine and hypothesized that the short term increase in thyroid hormone levels after ^{131}I therapy may be caused by discontinuation of ATD rather than ^{131}I itself. However, studies on patients who did not receive pre-treatment with ATD have shown elevated thyroid hormone levels after administration of ^{131}I.[25,26] Clerc *et al.*[27] retrospectively reviewed the records of 224 patients with diffuse goitre treated with ^{131}I; 107 of these patients received carbimazole for at least 3 weeks before and 2 weeks after radioiodine therapy. The remaining 117 patients received only radioiodine therapy. They found a higher failure rate in the subgroup treated with carbimazole but a lower rate of early onset hypothyroidism. After one year, the incremental rate of 4.5% of hypothyroidism was the same in both groups. Adjunctive drug therapy requires higher doses of ^{131}I due to the induction of radioresistance by ATD.[28,29] However, appropriate adjustment of the dose of ^{131}I would not affect the cure rate. In the light of available evidence, the use of ATD prior to and/or following ^{131}I therapy has to be individualized based on the age of the patient, the

severity of thyrotoxicosis and other co-morbid conditions. Since clinically significant exacerbations are uncommon in younger patients, ATD may be selectively administered to those in whom exacerbation might be hazardous such as patients who are ≥60 years of age or those with coronary artery disease.

Monitoring and follow up

Patients should be reviewed 6 to 8 weeks after ^{131}I therapy. The thyroid stimulating hormone (TSH) may remain suppressed for several months following radioiodine therapy. Therefore, at the initial follow up at 6–8 weeks both free T4 and TSH levels should be measured. If these results suggest a euthyroid state, the tests should be repeated at 12 weeks. If the results suggest hypothyroidism, there is a need to establish whether it is transient or permanent. Hypothyroidism developing in the early months after ^{131}I treatment may be transient[30] and replacement of thyroxine should be individualized. A useful practice is to give replacement thyroxine therapy to those with low free T4 irrespective of the TSH level. Further follow up of patients is essential as hypothyroidism can occur in 24%–90% of them. Free T4 and TSH levels can be repeated at arbitrary intervals of 6–12 months.[31] If the results at six months post-radioiodine therapy suggest persistent hyperthyroidism, a second dose may be considered. It is empirically suggested that the dose of radioiodine for retreatment would be 20%–30% higher than the initial dose. Leslie *et al.*[32] studied the outcome of retreatment with radioiodine for Graves' hyperthyroidism. They found that previous radioiodine therapy failure did not lessen the chance of successfully treating Graves' hyperthyroidism with additional radioiodine therapy. They also found no need for an increase in the dose of radioiodine in retreatment.

CURRENT PRACTICES

There is wide variation in the current practice in different geographical areas.

United Kingdom

The Royal College of Physicians recommends the use of radioiodine in all patients with hyperthyroidism, except those who are pregnant or lactating.[31] It cautions against the use of radioiodine in children less than 10 years of age. The College disagrees with the concept of administering a single large dose that results in rapid hypothyroidism. It suggests a range of 400 to 550 MBq (1 mCi=37 MBq) to achieve euthyroidism in 3–4 weeks, accepting a moderate rate of hypothyroidism, i.e. 15%–20% at two years and 1%–3% per annum thereafter.

USA

Solomon *et al.*[33] surveyed thyroidologists (n=197) in the USA regarding the choice of therapy for an index case of Graves' disease. Seventy per cent of them chose radioiodine as first-line therapy for an index case of a 43-year-old woman with Graves' disease and almost all of them preferred a single maximum dose. When the index case was a 19-year-old woman, only 33% preferred to use radioiodine. The authors concluded that the preference for radioiodine could be due to its cost-effectiveness and quick results. The rationale for the use of a large single dose is that attempting to achieve permanent euthyroidism with radioiodine is nearly impossible. A similar study in the USA[34] also found that many centres did not use radioiodine in patients below the age of 17 years.

India

A survey carried out by Mithal *et al.*[35] (n=32) found the approach among Indian thyroidologists to be different from those of their counterparts in North America. Only 28% perferred radioiodine in an index case of a 40-year-old women with Graves' disease. This showed an overall reluctance on the part of specialists in India to use radioiodine therapy. This trend—contrary to the practice in the West and the available scientific evidence—is possibly because of limited availability of radioiodine, an unrealistic risk perception and the lack of prospective trials in the Indian setting to evaluate the efficacy of different modalities of treatment to produce lasting remission.

SEQUELAE TO RADIOIODINE THERAPY

Acute radiation thyroiditis occurs within 2 weeks after exposure to ^{131}I, and may result in pain and tenderness over the gland. Occasionally, transient thyrotoxicosis may occur due to release of stored thyroid hormones. This acute exacerbation is unlikely with doses up to 13 mCi or a radiation dose up to 320 Gy.[36]

Hypothyroidism

There is a strong linear correlation between the radiation dose to the thyroid from radioiodine and the probability of developing hypothyroidism above a lower dose limit of 25 Gy.[37] Graves' disease is an autoimmune condition with a tendency to spontaneous hypothyroidism at the rate of 0.7% per year.[38] Patients with Graves' disease seem to have twice the radiosensitivity compared to normal subjects and hence the chance of developing hypothyroidism per unit of radiation received also doubles, reflecting a potentiating interaction between the underlying autoimmune disorder and radiation.[38] The rate of development of hypothyroidism following ^{131}I therapy is related to the dose. Lowe *et al.*[39] reported a 19% incidence of hypothyroidism after a single dose of 2.5 mCi. Ten mCi produced hypothyroidism in 50% of patients at 3 months and 69% at 1 year.[40] Safa *et al.*[41] reported that 90% of patients treated with ^{131}I at a mean thyroid dose of 160 Gy would develop hypothyroidism a year later. When the dose administered is 40 Gy, the incidence is 14% at 5 years and 27% at 10 years. When the dose is doubled to 80 Gy the incidence is 25% and 36% at 5 and 10 years, respectively. In calculating the appropriate ^{131}I dose to treat hyperthyroidism it is important to bear in mind that hypothyroidism follows sooner or later in nearly all patients treated with ^{131}I. Early onset of hypothyroidism is related to the dose,[42,43] but delayed hypothyroidism develops at about the same rate regardless of the amount of ^{131}I given.[44–46] The available evidence shows that hypothyroidism can be caused by the smallest therapeutic doses and the incidence continues to rise irrespective of the dose.

Ophthalmopathy

Radioiodine has been reported to be associated with a high incidence of development or exacerbation of Graves' ophthalmopathy (GO). The occurrence of eye disease might reflect the natural history of ophthalmopathy that usually has its onset within 18 months of the onset of Graves' disease.[47] The temporal relationship between radioiodine and exacerbation of ocular disease has led to a high suspicion for a causative role for ^{131}I. The relation between treatment of Graves' disease and eye disorder is unclear and is further complicated by the observation that the natural course of GO is highly variable with unpredictable exacerbations and remissions.[48] The pathogenesis of GO is uncertain and has been attributed to the thyroid tissue being a source of the antigen.[49]

Kriss *et al.*[50] reported the worsening of GO following radioiodine, the earliest report indicating the association between the two. This has been confirmed by other studies also.[51,52] Tallstedt

et al.[53] studied 168 patients with Graves' disease and found that the treatment modality used, pre-treatment T3 concentration and degree of lymphocytic infiltration of the thyroid were significant factors that could predict the development of GO. They concluded that compared to other forms of antithyroid therapy, ^{131}I is more likely to be followed by the development or exacerbation of GO. It is likely that high T3 levels indicate the presence of severe metabolic or immunological disturbances that predispose a patient to GO.[54] It has also been suggested that post-treatment hypothyroidism is important in the development of GO.[55]

Bartalena *et al.*[56] conducted a prospective single-blind, controlled study where radioiodine therapy was followed by development or progression (more often) of ophthalmopathy in patients treated with radioiodine alone but not in those treated with radioiodine and prednisolone. Patients treated with methimazole had no progression of eye disease. The authors concluded that the transient worsening of ophthalmopathy could be prevented by pre-treatment with prednisolone.

Kung *et al.*[57] evaluated the role of methimazole (which has an immunomodulatory action) in the prevention of GO in patients with Graves' disease who are given radioiodine therapy. They found that hypothyroidism or elevated TSH was associated with an increased risk of development or exacerbation of GO. They postulate that the reason for the higher incidence of GO after radioiodine therapy compared with other antithyroid treatment could be that patients are allowed to be in a hypothyroid state for a longer period, to distinguish between transient and permanent hypothyroidism. Manso *et al.*[58] evaluated the effect of treatment with radioiodine or ATDs (propyl thiouracil or methimazole) on ophthalmopathy. They did not observe any worsening of ophthalmopathy in either group. In fact, they found an improvement in the clinical signs of ophthalmopathy in 59% of patients treated with radioiodine and in 37.5% of patients treated with ATDs. According to these authors, maintenance of euthyroidism was the key to the outcome of ophthalmopathy after therapy.

Gorman[59] has hypothesized that post-radioiodine GO is more of a temporal than causative relationship and states that all therapeutic modalities simply treat hyperthyroxinaemia and the ability of the thyroid to produce thyroid hormones and none of them affect the underlying process which induces both hyperthyroidism and ophthalmopathy. DeGroot *et al.*[60] felt that radioiodine ablation may mitigate GO—an idea also put forward by Bauer and Catz.[61]

Radioiodine and leukaemias

All radiation is potentially carcinogenic and leukaemia is one of the most prominent late effects of exposure to ionizing radiation. However, there is no increased risk of leukaemia in subjects who receive ^{131}I for diagnostic or therapeutic purposes.[62] The Cooperative Follow up Study[63] addressed this issue. Out of 18 379 patients treated with radioiodine 17 developed leukaemia, whereas 16 out of 10 731 patients who were operated developed leukaemia. This study concluded that there was no evidence to support the hypothesis that radioiodine caused leukaemia. Some other studies also do not suggest any added risk of leukaemia with radioiodine.[64–66]

Thyroid cancer and solid tumours

Except for one case report,[67] several studies undertaken to detect an association between radioiodine and thyroid cancer have failed to detect any.[68–70] There is no evidence of an increased incidence of thyroid cancer in patients who have received radioiodine. Cancer in other organs is no more common in patients treated with radioiodine.[70,71] Similarly, in the few studies available in children and adolescents who received ^{131}I for thyrotoxicosis, the incidence of thyroid cancer, leukaemia or other cancers was not increased.[72–74]

RADIOIODINE THERAPY: CONCERNS IN SOME SPECIAL GROUPS

Use of radioiodine in children, adolescents and adults in the reproductive age group has caused some concern regarding infertility in the recipient and possible genetic abnormality or congenital anomalies in the offspring of the recipient. Hyperthyroidism *per se* may reduce fertility in women and definitive therapy of hyperthyroidism may help in improving the chances of conception. There is evidence that radiation from ^{131}I in the treatment of Graves' disease does not reduce fertility in either sex. Safa *et al.*[73] followed up 43 women who received radioiodine during childhood. There was no increase in congenital abnormalities in the 86 children born to these women during the follow up period. Gonadal radiation is of particular concern. The ovaries receive less than 3 rads (0.03 Gy) per 10 mCi of administered radioiodine and this dose is similar to that from several commonly performed radiological procedures such as a barium enema or intravenous pyelography. The calculated risk of genetic abnormalities is 0.003% or less and far less than the spontaneous rate of genetic abnormalities which is 0.86%.[74] Review of the evidence shows that radioiodine therapy for thyrotoxicosis has no adverse effects on the health of the offspring of treated patients.[13]

Children

In children, ATDs are often used as the primary modality of therapy for Graves' hyperthyroidism. Failure of ATDs to control the disease, hypersensitivity or idiosyncratic reactions to ATDs are indications where definitive therapy is warranted. The chances of lasting remission with ATDs are less than 50%. Hyperthyroidism in children is associated with behavioural problems.[75] The other drawbacks include non-compliance (particularly in adolescents), toxicity and enlargement of the goitre. In these situations definitive therapy with radioiodine or surgery is being increasingly favoured. A number of publications show ^{131}I therapy to be effective and safe in children.[74,76,77–81]

CONCLUSIONS

Graves' disease is the commonest cause of hyperthyroidism. The chief therapeutic objective is to alleviate the patient's thyrotoxicosis. We have placed the available information on the role of radioiodine in the treatment of Graves' hyperthyroidism and addressed various concerns and risk perceptions of patients as well as physicians. In most clinical situations, a strong argument can be made for radioiodine therapy, which is safe and definitive, although post-treatment hypothyroidism and the need for lifelong thyroxine are to be expected.

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