

## Treatment of hyperthyroidism

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*There are many clinical forms of hyperthyroidism. It is necessary to determine the specific cause in order to direct the treatment strategy accordingly. The most common form is Graves' disease, an autoimmune disorder characterized by the presence of thyroid stimulating immunoglobulin that binds to and stimulates the thyrotropin receptors resulting in thyroid overactivity. Toxic nodular goitres, the next highest in prevalence, cause hyperthyroidism due to autonomous hyperfunctioning thyroid nodules.*

*The therapeutic approaches to hyperthyroidism are 1) antithyroid drugs to block hormone synthesis and release, 2) surgery and 3) radioiodine ablation of thyroid tissue. All of these therapeutic modalities are effective but the latter two methods are probably the more definitive means to achieve remission of the hyperthyroidism.*

*Antithyroid drug therapy is the preferred treatment for children with Graves' disease and patients with small goitres and short disease durations. However, long term remissions from antithyroid drug treatment is approximately 50 %.*

*Surgery is an appropriate for a patient who has a very large goitre with symptoms of compression in the neck, or a patient with a cold nodule depicted on thyroid scan.*

*Currently radioiodine therapy is the most common therapy for Graves' disease. It is increasingly used as first-line therapy especially in elderly patients. It is the treatment of choice for patients with recurrent hyperthyroidism after antithyroid drug or surgical treatment. Radioiodine is also the preferred treatment for toxic nodular goitre. It is effective, safe and*

*low cost. However it may aggravate Graves' ophthalmopathy. The only major disadvantage is a high incidence of hypothyroidism. It is crucial that the patient be followed with annual post treatments so that hypothyroidism can be detected early and proper treatment initiated.*

**Key words:** *Hyperthyroidism, Graves' disease, Antithyroid drug, Radioiodine.*

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โรคต่อมธัยรอยด์เป็นพิษมีหลายชนิด จำเป็นต้องวินิจฉัยว่าเป็นชนิดไหน เพื่อให้การรักษาที่ถูกต้อง ชนิดที่พบบ่อยที่สุดคือโรค Graves ซึ่งเกิดจากความผิดปกติของระบบภูมิคุ้ม โดยพบว่าภูมิคุ้มในกลอบบูลินไปจับและกระตุ้นธัยโรโทรปินรีเซปเตอร์ เป็นผลให้ต่อมธัยรอยด์ทำงานมาก ชนิดที่พบรองลงมาคือโรคต่อมธัยรอยด์เป็นพิษชนิดเป็นก้อน ซึ่งพบบ่อยในถิ่นที่ขาดไอโอดีน อาการเป็นพิษนั้นเกิดจากก้อนในต่อมธัยรอยด์ทำงานมากกว่าปกติโดยอัตโนมัติ

การรักษาโรคต่อมธัยรอยด์เป็นพิษมี 3 วิธี คือ 1) ให้ยาด้านธัยรอยด์เพื่อไประงับการสร้างและปล่อยฮอริโมน 2) การผ่าตัด และ 3) ให้สารกัมมันตรังสีไอโอดีนเพื่อทำลายเนื้อเยื่อของต่อมธัยรอยด์ การรักษาใช้ได้ผลทั้ง 3 วิธี แต่สองวิธีหลังได้ผลแน่นอนกว่า

ยาด้านธัยรอยด์นิยมใช้ในเด็กทุกราย และผู้ใหญ่ที่ต่อมธัยรอยด์โตไม่มาก และเป็นโรคต่อมธัยรอยด์เป็นพิษได้ไม่นาน อย่างไรก็ตามการรักษาด้วยยาด้านธัยรอยด์ทำให้หายจากโรคได้ประมาณ 50% เท่านั้น

การผ่าตัดเหมาะสำหรับผู้ป่วยที่ต่อมธัยรอยด์โตมาก จนมีอาการแน่นที่คอ หรือผู้ป่วยที่มีก้อนในต่อมธัยรอยด์ซึ่งไม่จับสารกัมมันตรังสีในภาพสแกน

ปัจจุบันการรักษาโรค Graves ด้วยสารกัมมันตรังสีไอโอดีนเป็นวิธีที่ใช้กันมากที่สุด มีการใช้เป็นการรักษาอันดับแรกเพิ่มขึ้นเรื่อย ๆ โดยเฉพาะอย่างยิ่งในผู้ป่วยสูงอายุ และเป็นการรักษาที่เลือกใช้สำหรับผู้ป่วยที่เกิดโรคต่อมธัยรอยด์เป็นพิษซ้ำหลังจากได้รับการรักษาด้วยยาด้านธัยรอยด์ หรือการผ่าตัด สารกัมมันตรังสีไอโอดีนนิยมใช้มากขึ้นสำหรับรักษาโรคต่อมธัยรอยด์เป็นพิษชนิดเป็นก้อน การรักษาด้วยวิธีนี้อาจทำให้อาการทางตาเลวลง ข้อเสียสำคัญของการรักษาด้วยวิธีนี้คืออุบัติการณ์ของโรคต่อมธัยรอยด์ทำงานน้อยนั้น จะสูงกว่าการรักษาด้วยวิธีอื่น จึงจำเป็นมากที่จะต้องติดตามตรวจผู้ป่วยปีละครั้งตลอดไปภายหลังการรักษา เพื่อวินิจฉัยโรคต่อมธัยรอยด์ทำงานน้อยแต่เนิ่น ๆ จะได้ให้การรักษาที่เหมาะสมต่อไป

Hyperthyroidism has many causes that can be classified according to the sources of the excess thyroid hormone. It is essential to distinguish thyrotoxic state that results from primary thyroid hyperfunction and those without hyperactivity in order to direct treatment effectively.

The most common form of hyperthyroidism is Graves' disease which is an autoimmune disease characterized by the presence of thyroid stimulating immunoglobulin (TSI) that binds to and stimulates the thyrotropin (TSH) receptors resulting in thyroid overactivity.<sup>(1,2)</sup> The next most common form of hyperthyroidism is toxic nodular goiter which is characterized by the increased secretion of thyroid hormone by autonomous solitary or multiple thyroid nodules within the thyroid gland. It is more common in iodine deficient region. Other forms of hyperthyroidism are relatively uncommon and will not be discussed in this presentation. Graves' disease is the focus of this discussion.

#### Choice of treatment

The therapeutic approaches to hyperthyroidism are antithyroid drugs (ATD), surgery and radioactive iodine (RAI). All are effective but no single method offers permanent euthyroidism. There is considerable disparity of opinion regarding the first choice for patients with Graves' disease.<sup>(3-5)</sup> Each modality has its own indications, contraindications, advantages and disadvantages. Guidelines are available to assist in making an appropriate choice for each patient.<sup>(2,6)</sup> However, the use of RAI as first-line therapy for hyperthyroidism is growing, especially at our institute and in some other places.<sup>(6)</sup> It is the most common therapy in the United States.<sup>(4,7)</sup> Whatever approach

is selected, beta-adrenergic blocking agents are used in the early symptomatic phase of hyperthyroidism to control adrenergic manifestations.<sup>(2)</sup>

#### Medical therapy

##### Thionamide drugs and mechanism of action

The most commonly used thionamide drugs are propyl thiouracil (PTU) and methimazole. Their principal action is to inhibit the organification of iodide and coupling of iodothyronines which in turn suppresses the synthesis of thyroid hormones. PTU has an additional peripheral effect that inhibits the conversion of thyroxine (T4) to tri-iodothyronine (T3).<sup>(8)</sup> This effect probably inspires a preference for PTU rather than methimazole by some thyroidologists. All thionamide drugs also have a beneficial immunosuppressive effect that reduces the TSH receptor antibody concentrations which suppress the immune-mediated hyperthyroidism of Graves' disease.<sup>(2,9,10)</sup>

Propyl thiouracil is the preferred treatment for pregnant and lactating patients as it binds strongly to protein which makes their passage across the placenta or into breast milk limited.<sup>(2,11)</sup>

The half-life of methimazole in plasma is three to five hours, and that of PTU one to three hours.<sup>(12)</sup> In addition, methimazole has approximately 10 times the potency of PTU on a weight basis, therefore, PTU requires greater frequency of dosing and a greater number of tablets per dose, making patient compliance more difficult.<sup>(2)</sup>

##### Indications and treatment regimens

Indications for ATD therapy include hypothyroidism in children and patients with mild symptoms, small goiters and short disease duration.

The initial dose of ATD is usually 200 to 600 mg of PTU per day in three or four divided doses or 20 to 60 mg of methimazole per day in single or divided doses. The maintenance dose is 50 to 150 mg of PTU or 5-15 mg of methimazole daily. The treatment is usually continued for 12 to 18 months.<sup>(2,6,11)</sup>

#### Outcome of treatment

Remission rates after ATD therapy are usually low. After a 12 month course of ATD therapy, the remission rate is approximately 50%.<sup>(2,13)</sup> Relapse is most likely within the first six months after withdrawal from ATD but may also occur several years later.<sup>(14)</sup>

#### Side effects

The most common side effects are mild allergic reactions such as skin rash, pruritus, fever, transient leukopenia. The most serious side effect is agranulocytosis which occurs in 0.1-0.5% of patients and is most commonly manifested during the first 3 months of the therapy.<sup>(2,11,15)</sup> Permanent hypothyroidism occurs in about 0.6% of cases per year after ATD treatment.<sup>(16)</sup>

#### Surgical treatment

##### Indications and contraindications

Currently, thyroid surgery is rarely used to treat patients with Graves' disease. The major indications for surgery are large nodular goiters, very large goiter causing pressure symptoms in the neck, or patients with a nonfunctioning nodule on scintigraphic scan. The risk of malignancy in the nodule is much greater than in euthyroid subjects and the carcinoma tends to be more aggressive.<sup>(17)</sup> Surgery is also applied after antithyroid drug therapy

failure and if the patient refuses radioiodine therapy. Contraindications include severe concurrent disease, e.g., heart, lung and previous thyroid surgery.

The usual surgical approach is subtotal thyroidectomy in order to leave sufficient tissue to preserve the parathyroid and recurrent laryngeal nerves. To avoid serious complications, it is important to refer the patient to a skilled surgeon. Prior to surgery, patients should be treated with ATD until euthyroid. The use of  $\beta$ -blockers alone is not an adequate preparation.<sup>(6)</sup>

#### Results of treatment

The advantages of surgery include rapid reversal of hyperthyroidism and high cure rates. At 1 year after surgery, approximately 80% of patients become euthyroid, but permanent hypothyroidism occurs in 5 to 75%. The prevalence of hypothyroidism increases with time.<sup>(6,18,19)</sup> Recurrent hyperthyroidism occurs in 1 to 3% of patients in the first year, but most often occurs during the first five years after surgery.<sup>(6,18)</sup>

#### Complications

The prevalence of complications depends on the skill of the surgeon. Apart from hypothyroidism which can be either transient or permanent, the specific post operative complications of thyroid surgery include damage to recurrent laryngeal nerves and hypoparathyroidism.<sup>(6,18)</sup>

#### Radioiodine therapy

Hyperthyroidism has been treated with iodine-131 for over 50 years.<sup>(20)</sup> Currently, radioiodine therapy is the most common therapy for Graves' disease. The cumulative experience of this therapy

has confirmed its efficacy, safety and cost-effectiveness.<sup>(2, 21)</sup> It is used increasingly as a first-line therapy for adults and as the treatment of choice for many clinical situations. At our institute, we have used iodine-131 for treatment of hyperthyroidism since 1959. Up to the end of 1998, a total of 13, 536 hyperthyroid patients had been treated. The patients with hyperthyroidism who were referred for radioiodine therapy during the last 5 years increased from 713 to 1240 cases per year.

The objective of radioiodine therapy is to destroy thyroid tissue sufficiently for rendering euthyroid. The treatment goal is to administer enough radiation to achieve euthyroidism without causing hypothyroidism unless it is the intention of the physician to induce hypothyroidism in some patients to avoid the risk of persistent hyperthyroidism. However, the most appropriate dose schedule remains controversial.<sup>(6, 18, 21)</sup>

#### Indications and contraindications

There is general agreement that radioiodine therapy is the treatment of choice for hyperthyroidism in the elderly, cases of recurrence after thyroid surgery or medical therapy and severe concurrent disease, e.g., heart, lung, or chronic renal disease. Currently, the indications for radioiodine use includes young patients above a preselected age.<sup>(2, 6)</sup> At our institute, we consider use of radioiodine for patients over age 25. Several investigators reported their experiences in the use of radioiodine therapy in children and adolescents.<sup>(22-24)</sup> Most clinics are reluctant to use I-131 therapy in children and adolescents although concerns about radiation-induced malignancy, mutagenic effects in offspring or impaired fertility have

not been confirmed.<sup>(2, 18)</sup>

Pregnancy and breast feeding mothers are absolutely contraindication for radioiodine therapy. Other contraindications are suspected coexisting malignancy, patients below a preselected age limit and patients who fear radiation. The use of radioiodine in patients with significant ophthalmopathy remains contentious.<sup>(2, 6)</sup>

#### Patient preparation

Radioiodine therapy requires no medical preparation for most patients. However, in high-risk patients with severe hyperthyroidism and with complications, especially cardiovascular diseases and elderly patients, it is necessary to render the patients euthyroid with antithyroid drugs prior to radioiodine therapy to avoid the possibility of exacerbation of the disease due to hormone release after radiation.<sup>(6, 21)</sup> We usually gave high dose antithyroid drug for 4-6 weeks to bring the patient to euthyroid status and stopped the drug for one week before administering I-131. However the medication can be discontinued as briefly as 48-72 hours before radioiodine therapy or continued at a reduced dose during therapy.<sup>(25)</sup> Continuing therapy with thionamides is prescribed 5-7 days after the administration of radioiodine. In patients with severe symptoms, a beta-blocker may be added to the pretreatment regimen. Digoxin should also be used in those patients with atrial fibrillation or heart failure.<sup>(21)</sup>

#### Dose consideration

The most widely used method is to calculate the radioiodine dose in microcuries ( $\mu\text{Ci}$ ) per gram of thyroid tissue. The calculation requires an estimated

thyroid weight, the dose to be delivered per gram and the 24-hour thyroid uptake. Some clinics attempt to get a more precise estimated thyroid mass with ultrasonography. The following formula is generally used for I -131 dose calculation: <sup>(2, 11, 18, 25)</sup>

$$\text{Administered } \mu\text{Ci} = \frac{\mu\text{Ci/g desired} \times \text{estimated gland wt(g)} \times 100}{24\text{-hour radioiodine uptake (\%)}$$

The desired dosage in microcuries to be delivered per gram of thyroid ranges from 50 to 200  $\mu\text{Ci}$  (1850 to 7400 kBq). <sup>(2, 11, 18, 25)</sup> The radiation dose can be classified as low-dose (50-80  $\mu\text{Ci}$  or 1,850 – 2,960 kBq) medium-dose (100-120  $\mu\text{Ci/g}$  or 3,700-4,400 kBq) and high dose (150-200  $\mu\text{Ci/g}$  or 5,550-7,400 kBq).

We prefer to use low doses for hyperthyroid patients with short disease duration, small goiters and young patients, especially the males because their thyroid gland is more sensitive to radioiodine.

The medium dose is most widely used for the majority of patients with moderately severe hyperthyroidism. Higher doses of radioiodine are suggested for patients with rapid radioiodine turnover, large goiters and those receiving antithyroid drugs before radioiodine therapy. This is because larger glands and prior antithyroid therapy induce more resistance to the radioiodine. <sup>(2, 26, 27)</sup>

High or ablative doses of radioiodine are generally prescribed for severely hyperthyroid patients or those with underlying cardiac or other serious diseases or in elderly patients in whom the risks of persistent hyperthyroid are to be avoided. The associated higher incidence of hypothyroidism may be an acceptable consequence in such cases. <sup>(18, 25, 26)</sup>

Some author advocates ablative doses of radioiodine for patients with ophthalmopathy in order to eliminate any possibility of recurrence. <sup>(26)</sup> However, radioiodine therapy should be postponed in patients with progressive ophthalmopathy until their eye disease becomes stable by antithyroid drug therapy. <sup>(28)</sup>

Toxic adenoma or toxic multinodular goiter are more radioresistant; therefore, the high – dose method is commonly employed. <sup>(26, 27, 29)</sup>

### Results of therapy

Usually, hyperthyroid symptoms improve within 2 to 4 weeks after radioiodine therapy. However, the full clinical impact may not be achieved until 3 months after therapy. The majority of patients require no supplemental therapy during this period. Our experience has shown that about 75% of hyperthyroid patients were cured with one dose of I-131. <sup>(30)</sup> Once euthyroid status has been achieved, hyperthyroidism rarely recurs. <sup>(28)</sup> Hypothyroidism occurring within the first six months after treatment may be transient or permanent. About 5 % of our patients developed transient hypothyroidism, and most of them spontaneously returned to normal within 3 to 6 months. If a patient is treated with thyroxine, reassessment for continued therapy should be done after 6 months. For persistent hyperthyroidism, repeat I -131 treatments should be considered at least 3 months after the first dose.

### Adjunctive medication

#### *Beta-Adrenergic Blocking Agents*

Beta-adrenergic blocking agents (propranolol, atenolol, metoprolol, nadolol, etc.) ameliorate some of the peripheral manifestations of hyperthyroidism

through action on  $\beta$ -adrenergic receptors.<sup>(28)</sup> The major clinical effects by these drugs include reduction in heart rate and relief of palpitations. Beta-blocking agents are particularly useful for moderate or severe hyperthyroid patients since they make the patient more comfortable but do not interfere with most diagnostic tests or radioiodine therapy.<sup>(25, 28)</sup> The usual dose of propranolol is 20-40 mg, 3 to 4 times a day,<sup>(25)</sup> or atenolol 50-100 mg once a day.<sup>(28)</sup> Propranolol may be contraindicated in some patients with congestive heart failure or asthma, atenolol or metoprolol may be used with care in patients with asthma.<sup>(25)</sup>

#### ***Thionamides***

Thionamide may be used to control hyperthyroidism in elderly patients with moderate or severe symptoms or patients with cardiac disease. When euthyroid status is achieved, the antithyroid drug should be tapered off and eventually discontinued, and the thyroid status should be evaluated.

#### ***Stable iodine (I-127)***

Inorganic iodine given in pharmacologic doses, as Lugol's solution or as a saturated solution of potassium iodide (SSKI), inhibits the release of thyroid hormones. This agent will reduce levels of circulating hormones faster than thionamides; therefore, it may be useful for rapid control of hyperthyroid symptoms following radioiodine treatment in patients with mild to moderately severe hyperthyroidism.<sup>(25, 28)</sup> The usual dose of Lugol's solution is 0.1 to 0.3 ml three times daily, and that of SSKI is one drop three times daily.<sup>(11, 28)</sup> It can be started one week after radioiodine treatment and continued until the symptoms of thyrotoxicosis resolve. Transient hypothyroidism was common in

patients who received iodine, and it disappears rapidly when the iodine is withdrawn.

Stable iodine may be used in patients in whom a partial response is achieved by I-131 but, where mild hyperthyroidism still persists. Radioiodine treated glands seem particularly sensitive to iodides and this sensitivity may persist for months or years.<sup>(31, 32)</sup> About one to three drops of saturated potassium iodide solution per day are quite effective to control hyperthyroid symptoms.

#### ***Lithium***

Lithium may prolong the retention of radioiodine thus enhance its effect.<sup>(33, 34)</sup> We often use the drug as an adjunct therapy for patients with rapid radioiodine turnover.

#### **Side effects**

##### ***Exacerbation of hyperthyroidism***

Transient worsening of hyperthyroidism may occur within the first two weeks after radioiodine therapy but it rarely occurs in patients with adequate pretreatment with antithyroid drugs. This exacerbation is caused by radiation thyroiditis and can be severe if a high ablative dose of I-131 has been given to a patient with a large overactive gland.<sup>(26)</sup> Thyroid crisis is a rare complication and should not occur if the most severely toxic patients are pretreated with antithyroid drugs and beta-blockers prior to radioiodine therapy.<sup>(35)</sup>

##### ***Ophthalmopathy***

Graves' ophthalmopathy can occur before, during or after radioiodine treatment. Whether Graves' ophthalmopathy will deteriorate after radioiodine therapy is controversial.<sup>(2, 25, 28)</sup> However, a recent study reported a significantly increased risk (33 %) of new



or worsening orbitopathy in patients treated with radioiodine compared to those treated with surgery (16 %) or antithyroid drugs (10 %).<sup>(36)</sup> With current consensus that Graves' ophthalmopathy is the result of an immunologic attack on the orbit, because of some antigens shared with the thyroid, the removal of thyroid antigen becomes more sensible.<sup>(37)</sup> Thyroid ablation by radioiodine may in the long run prove to be beneficial influencing the immunological mechanisms of Graves' ophthalmopathy through the removal of the source of antigen.<sup>(5,38,39)</sup> Radioiodine-associated exacerbation of eye disease can be prevented by concomitant administration of glucocorticoids.<sup>(6,38,40,41)</sup>

#### *Hypothyroidism*

The only important complication of radioiodine therapy is the development of permanent hypothyroidism which may occur at any time after treatment. It is generally accepted that hypothyroidism is inevitable in patients with Graves' disease treated with I -131. Therefore, life-long follow-up of patients is crucial after radioiodine therapy. After treatment all patients should be followed annually so that hypothyroidism can be detected early and proper treatment initiated.

Hypothyroidism mostly occurs in the first 2 years following both surgery and radioiodine.<sup>(25)</sup> Various studies have shown that about 20 to 64% of patients became hypothyroid about 1 year after treatment. Subsequently, hypothyroidism appeared at a relatively constant rate of 3-5 % per year after radioiodine treatment.<sup>(1, 11, 25)</sup> The late onset of hypothyroidism or cumulative hypothyroidism is not directly related to the amount of radioiodine received by the thyroid gland.<sup>(40,41)</sup> Many think that

in some patients, hypothyroidism is part of the natural history of Graves' disease.<sup>(11)</sup> It is noted that hypothyroidism is a frequent result of successful radioiodine or surgical ablation.<sup>(2)</sup>

Toxic multinodular goiters and toxic adenoma treated with I -131 less often lead to hypothyroidism. This is due to the suppression of normal thyroid tissue by the hypersecretion of autonomic hyperfunctioning tissue.<sup>(29,35)</sup>

#### **Follow-up**

Thyroid functions should be evaluated at 2-3 months intervals after radioiodine administration or more frequently if the patient is on antithyroid drug. When euthyroid has been achieved, thyroid status should be monitored annually thereafter life-long. Appropriate thyroid function tests include serum T3, T4 or free T4 and sensitive TSH. Although the serum TSH is most sensitive in the evaluation of thyroid function, it should be kept in mind that the serum TSH levels may remain suppressed for several weeks or even months after the patient is euthyroid, so it is not a reliable monitor to follow in the first few months.<sup>(18,25)</sup> Because transient hypothyroidism is not uncommon, it is generally recommended that patients should not be started on T4 therapy within 6 months unless they have clinical signs and symptoms of hypothyroidism.<sup>(18)</sup> It is important to demonstrate clearly that a patient has non-recoverable hypothyroidism before committing the patient to lifelong thyroxine treatment.<sup>(31)</sup>

#### **Conclusions**

Selection of the appropriate mode of treatment for hyperthyroidism depends on various factors

such as patient's age, disease severity, patient's preference, etc. Radioiodine therapy is most commonly used, most effective, simple and is a safe method in the treatment of hyperthyroidism, but it carries a high risk of developing hypothyroidism. After successful treatment with any method, lifelong follow-up is necessary.

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