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Hyperthyroidism
Current Treatment Guidelines

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Contents

Summary

Hyperthyroidism is common and affects approximately 2% of women and 0.2% of men. The most common cause of hyperthyroidism is Graves' disease, an autoimmune disorder associated with circulating immunoglobulins that bind to and stimulate the thyrotropin (TSH) receptor, resulting in sustained thyroid overactivity. Toxic nodular goitres cause hyperthyroidism due to autonomous hyperfunctioning of localised areas of the thyroid.

There are 3 recognised modalities of treatment for hyperthyroidism: antithyroid drugs, surgery and radioiodine. All are effective but no single method offers an absolute cure. Patients with Graves' disease may be prescribed antithyroid drugs over a period of 12 to 18 months with a view to inducing a long term remission. These drugs are also often given for a short period to render the patient euthyroid before definitive therapy with radioiodine or thyroidectomy. However, antithyroid drugs will not 'cure' hyperthyroidism associated with a toxic nodular goitre.

The use of radioiodine as a first-line therapy for hyperthyroidism is growing.

It is well tolerated, with the only long term sequelae being the risk of developing radioiodine-induced hypothyroidism. Radioiodine can be used in all age groups other than children, although it should also be avoided in pregnancy and during lactation. Pregnancy should be avoided for 4 months following its administration. Radioiodine may cause a deterioration in Graves' ophthalmopathy and corticosteroid cover may reduce the risk of this complication. The treatment of choice for toxic nodular goitre hyperthyroidism is radioiodine.

Surgery, either subtotal or near-total thyroidectomy, has limited but specific roles to play in the treatment of hyperthyroidism: this approach is rarely used in patients with Graves' disease unless radioiodine has been refused or there is a large goitre causing symptoms of compression in the neck. The goal of surgery is to cure the underlying pathology while leaving residual thyroid tissue to maintain postoperative euthyroidism.

1. Establishing the Diagnosis of Hyperthyroidism

1.1 History and Physical Examination

Hyperthyroidism is common and affects approximately 2% of women and 0.2% of men.[1] The classical symptoms and signs of thyrotoxicosis are listed in table I. In some elderly patients, however, the hyperactive symptoms and signs may not be apparent (apathetic thyrotoxicosis), with the major features being anorexia, bodyweight loss, cardiac failure, palpitations and, in 10% of cases, atrial fibrillation.[2,3]

It is important to determine the specific cause of the thyrotoxicosis as it is the aetiology that dictates treatment strategy. The most common cause of thyrotoxicosis is Graves' disease (table II lists other causes) and a clinical diagnosis can be made if diffuse enlargement of the thyroid and ophthalmopathy are present. Toxic nodular goitres tend to occur in an older age group and are not associated with ophthalmopathy, and examination of the neck reveals a nodularity within the enlarged thyroid (see table III).

Clinical signs of thyrotoxicosis that are of recent onset, along with a history of a recent viral illness with swelling and tenderness of the neck, may indicate subacute thyroiditis. Symptoms and signs of thyrotoxicosis, without ophthalmopathy, but with a pregnancy within the preceding 12 months, make the diagnosis of postpartum thyroiditis possible.[4]

Table I. Symptoms and signs of thyrotoxicosis

Sweats	Palpitations
Flushing	Rapid bowel transit
Anxiety/nervousness	Irritability
Heat intolerance	Shortness of breath
Hair loss	Tremor
Bodyweight loss	Increased appetite
Muscle weakness (periodic paralysis rarely in Asians)	Sore/gritty/protruding eyes and double vision[a]
Goitre	Palmar erythema
Tremor	Tachycardia
Atrial fibrillation	Ophthalmopathy[a]
Vitiligo[a]	Onycholysis
Acropachy[a]	Pretibial myxoedema[a]
Myopathy	

a Graves' disease only.

1.2 Laboratory Investigations of Thyroid Function

An initial biochemical assessment of thyroid status should include measurement of serum free thyroxine (FT_4) and thyrotropin (TSH) levels. In the presence of hyperthyroidism, FT_4 is elevated and TSH is suppressed to below the levels of detection by modern sensitive TSH assays. If TSH is suppressed but FT_4 is within the normal range, a free tri-iodothyronine (FT_3) concentration should be measured as, if elevated, this finding indicates tri-iodothyronine toxicosis. With the availability of

Table II. Causes of thyrotoxicosis, associated pathogenic mechanisms, and frequency of occurrence

Cause	Pathogenesis	Occurrence
Graves' disease	Autoimmune	Very common
Toxic nodular goitre multiple nodules solitary toxic nodule	Autonomous functioning of thyroid	Common
Thyroiditis subacute silent postpartum	Release of thyroid hormones secondary to inflammatory process	Uncommon
Iatrogenic	Prescription of excess T_4 or T_3	Common
TSH-secreting pituitary tumour	Autonomous TSH secretion from pituitary	Very rare
Pituitary resistance to thyroid hormones	Very rare clinical condition of uncertain aetiology	Very rare
Neonatal hyperthyroidism	Transplacental passage of TSH receptor antibodies	Very rare
Exogenous iodide	Augmented thyroid secretion in patients with underlying thyroid autonomy	Very rare
Factitious hyperthyroidism	Ingestion of T_4 or T_3	Very rare
Rare malignancies	Thyroid cancer, choriocarcinoma, hydatidiform mole, embryonal testicular carcinoma, struma ovarii	Very rare

Abbreviations: TSH = thyrotrophin; T_3 = T_3-tri-iodothyronine; T_4 = T_4-thyroxine.

specific assays to measure free thyroid hormone levels, there is no indication for performing total thyroid hormone measurements, as these values are affected by changes in serum concentrations of thyroxine-binding globulin (TBG) – for example, in pregnant women, people taking estrogens or individuals with an inherited increase in the production of TBG. A significant titre of thyroid autoantibodies (including the pathogenic TSH receptor antibody) in a patient with hyperthyroidism strongly suggests the diagnosis of Graves' disease.

The very rare clinical entity of secondary hyperthyroidism due to a TSH-secreting anterior pituitary adenoma is characterised by thyrotoxicosis, elevated thyroid hormone concentrations and elevated or inappropriately normal levels of TSH. The serum glycoprotein hormone α-subunit concentration is also elevated in this condition and the diagnosis is confirmed by demonstrating a pituitary tumour on radiological imaging.

1.3 Thyroid Scanning

Thyroid uptake scans (iodine or technetium) are of use in determining the aetiology of thyrotoxicosis. Graves' disease, toxic multinodular goitre, toxic thyroid adenoma and subacute thyroiditis are usually obvious on clinical grounds, as mentioned above. If the cause is not apparent, however, thyroid scans can often determine the underlying pathology. Measurements of isotope uptake are also

Table III. Differentiating features of the commonest causes of thyrotoxicosis

	Graves' disease	Toxic nodular goitre	Thyroiditis
Goitre	Diffuse	Nodular (single, multiple)	Firm, tender
Ophthalmopathy	Present	Absent	Absent
Thyroid scan	Diffuse increased uptake	Focal area(s) of increased uptake	Reduced uptake
Treatment	Antithyroid drugs, β-blockers, radioiodine, surgery	β-Blockers, radioiodine, surgery, antithyroid drugs[a]	β-Blockers, nonsteroidal anti-inflammatory drugs[a], *not* radioiodine or surgery

a May be of use in the short term.

useful in distinguishing thyroiditis from true thyrotoxicosis. Diffuse uptake signifies Graves' disease, whereas focal areas of increased uptake indicate toxic nodular goitre.

2. Treatment of Hyperthyroidism

Treatment of hyperthyroidism may be directed at the underlying cause of the hyperthyroidism, the thyroid hypersecretion or the clinical manifestations of hyperthyroidism. With respect to the most common cause of hyperthyroidism, Graves' disease, only the latter 2 forms of treatment are currently feasible. Antithyroid drugs, radioiodine and surgery are all effective treatments of hyperthyroidism[5] but opinions vary regarding the indications for them as no single treatment guarantees permanent euthyroidism. A number of studies have shown that, among thyroid specialists around the world, there is considerable disparity of opinion regarding the first choice of treatment to use in a 'typical' patient with Graves' disease.[6-10]

3. Antithyroid Drugs (Thionamides)

3.1 Pharmacodynamics and Pharmacokinetics

The mainstay of pharmacological treatment of hyperthyroidism relies on 3 antithyroid drugs – thiamazole (methimazole), carbimazole and propylthiouracil (PTU). Carbimazole is a prodrug which is metabolised virtually completely to the active product, thiamazole, making the dose and effects of both drugs equivalent. All 3 antithyroid drugs act by inhibiting the organification of iodide and the coupling of iodothyronine residues which in turn suppress the synthesis of thyroid hormones. PTU has an additional peripheral effect that inhibits its conversion of T_4-thyroxine to the biologically active thyroid hormone T_3-tri-iodothyronine, by blocking the enzyme 5′ monodeiodinase.[11] There is also some evidence that antithyroid drugs have immunosuppressive effects which suppress the immune-mediated hyperthyroidism of Graves' disease.[12,13] The half-lives of the respective drugs necessitate that thiamazole and carbimazole be taken once daily, whereas PTU needs to be administered in divided doses (2 to 3 times daily),[14] making drug compliance a potential problem; for this reason, carbimazole or thiamazole is the drug of choice.

3.2 Adverse Effects and Use in Pregnancy

Thionamides are well tolerated drugs. The most serious adverse effect of all 3 thionamides is agranulocytosis, which occurs in approximately 3 per 10 000 patients receiving a thionamide per year.[15] All patients who are started on a thionamide should be warned of this potentially very severe (and sometimes fatal) complication. Patients are instructed to immediately stop taking their medication and seek medical attention and an urgent blood test should they develop a sore throat or other infection.

Most cases of agranulocytosis occur within the first 3 months of starting therapy and on doses of thiamazole 30mg or more.[16] This reaction is idiosyncratic, however, and can thus occur at any stage of treatment on any dose or even during a second course of treatment.[17] In assessing the white cell counts of such patients, it should be borne in mind that hyperthyroidism itself is associated with a mild neutropenia. Following an episode of agranulocytosis or another serious (but also rare) complication of therapy, such as hepatitis or a lupus-like syndrome, thionamides are absolutely contraindicated. Minor drug rashes and pruritus are common with thionamides but often resolve with continuing therapy. It is sometimes necessary, however, to change from carbimazole to PTU or *vice versa* due to these adverse effects, in which case the reaction recurs infrequently.

All thionamides are well tolerated in pregnancy although there are theoretical reasons for changing women over to PTU should they have intentions to conceive or be currently pregnant. First, there is a possible association between carbimazole therapy and the rare congenital abnormality of fetal aplasia cutis,[18-20] and furthermore, PTU is excreted in breast milk to a lesser degree than carbimazole.[21-23] Whichever thionamide is used, it is

likely that a dose reduction will be required during pregnancy due to the naturally immunosuppressive effects of pregnancy on the immune reaction in Graves' disease. Some physicians choose to completely withdraw antithyroid medication in the third trimester of pregnancy. Thionamides do cross the placenta and in high doses may cause fetal goitre and hypothyroidism. Pregnant women with hyperthyroidism should be reviewed monthly with tests of thyroid function, and dose adjustments should be made accordingly with the aim of maintaining euthyroidism throughout pregnancy using the lowest possible dose of thionamide.

3.3 Indications for the Use of Thionamides and Treatment Regimens

3.3.1 Induction of Remission of Graves' Disease

Thionamides are used over a protracted period of time in a patient with a first episode of Graves' hyperthyroidism, in the hope of inducing a long term remission. Carbimazole is prescribed at an initial dose of 20mg (40mg or higher in severe hyperthyroidism,[24] although higher doses are associated with more adverse effects;[25-27] equivalent doses of PTU are 10-fold greater than those of carbimazole, i.e. carbimazole 20mg has an equivalent effect to PTU 200mg) and this is titrated down according to clinical response and thyroid function tests performed approximately every 4 to 6 weeks at review.

The FT_4 level should guide dose adjustments as it is common for the TSH level to remain suppressed in the long term. An elevated TSH level, however, is an indication for reducing the dose of antithyroid medication. A maintenance dose is achieved (usually carbimazole 5 to 15mg) which keeps the patient clinically and biochemically euthyroid. Treatment is usually maintained for 12 to 18 months[28,29] after the free thyroid hormone levels have returned to the normal range. The duration of administration of antithyroid drugs is an important variable that affects the likelihood of remission. After 6 months' therapy, recurrence of Graves' disease has been documented in 69% of patients after 1 year follow-up, whereas the recurrence rate was 18% after the same follow-up interval in those treated for 2 years.[29] Despite a long duration of thionamide therapy, however, a long term remission rate of 50% is unlikely to be achieved.[30] Some of the variability in relapse rates following discontinuation of thionamide therapy is likely to reflect differences in oral iodine intake. As yet there are no reliable clinical, biochemical, immunological or genetic factors that have been identified that allow prediction of those patients likely to do well, or poorly, in achieving long term remission.[28,31,32-36]

Anecdotally, patients with large goitres and/or severe hyperthyroidism before the start of treatment are unlikely to achieve and maintain a long term remission with antithyroid drugs. Relapse is most likely within the first 6 months following discontinuation of antithyroid drugs but can occur years later. Approximately 15% of patients who receive medical therapy for Graves' disease develop hypothyroidism following discontinuation of thionamide medication. This observation reflects the observation that Graves' disease and Hashimoto's thyroiditis are at the extremes of an autoimmune process affecting the thyroid.

Evidence that antithyroid drugs have an immunosuppressive effect has led some clinicians to adopt a 'block and replace' regimen for treating Graves' disease, i.e. prescribing a combination of thionamide (equivalent to approximately carbimazole 40mg) and thyroxine (approximately 100 to 200μg).[37] This approach allows treatment with high doses of antithyroid medication without the risk of iatrogenic hypothyroidism. The 'block and replace' regimen is absolutely contraindicated in pregnant women due to development of fetal hypothyroidism. In 1991, a Japanese group published data suggesting that thyroxine therapy prescribed during and after conventional antithyroid drug therapy significantly reduced the risk of relapse of Graves' disease.[38] Other groups, however, have found no beneficial effect from such treatment.[39-42]

3.3.2 Short Term Therapy Prior to Definitive Radioiodine Treatment or Thyroidectomy

Before radioiodine therapy is administered or thyroid surgery performed, patients with moderate to severe hyperthyroidism should receive short term treatment with antithyroid drugs (6 to 8 weeks). Administration of radioiodine to an already overtly overactive thyroid gland can result in thyroid crisis.[43] The object of this treatment is to reduce the degree of hyperthyroidism, although it is unnecessary to wait for complete clinical and biochemical euthyroidism to be achieved. Equivalent starting doses to those used in long term therapy are prescribed in this situation. It is necessary to discontinue thionamide treatment approximately 5 days before administering radioiodine. Tuttle et al.[44] reported more treatment failures in patients who received antithyroid drugs prior to radioiodine (34%) than in those treated with radioiodine alone (4%), and thus larger doses of radioiodine are sometimes prescribed for those patients who have received recent antithyroid medication (within the last month). Some advocate that young patients (20 to 40 years) with 'moderate' hyperthyroidism may receive radioiodine with no adjunctive antithyroid medication,[45] the benefit being a potentially increased chance of first-dose cure.

Owing to the different aetiology of thyroiditis, thionamides are ineffective in the treatment of hyperthyroidism due to this group of conditions (see below).

4. β-Adrenoceptor Antagonists

β-Blockers should be considered as adjuvant treatment in all patients with moderate or severe hyperthyroidism. The usual cautionary advice still applies, however, in patients with asthma or cardiac failure (even if the latter is due to the thyrotoxic state). All β-blockers are equally effective in alleviating features of adrenergic hyperstimulation such as tachycardia and tremor. For compliance reasons, we tend to use once-daily formulations such as nadolol 80mg daily or atenolol 50 to 100mg daily. Continuation with β-blocker therapy is indicated until the patient is rendered biochemically euthyroid by other forms of treatment. The typically brief episode of thyrotoxicosis that is secondary to thyroiditis can normally be managed by the use of β-blockers alone.

5. Radioiodine

5.1 Indications and Contraindications

Radioiodine is the treatment of choice for hyperthyroidism in patients with toxic nodular goitre and those individuals who have suffered a relapse of Graves' disease following a full course of thionamide therapy. Currently, it is more frequently being used as a primary mode of treatment for Graves' disease, especially in the elderly, although it may be given to individuals in their late teens (usually 18 years and over, although all cases should be considered on merit) if necessary.

The use of radioiodine is contraindicated in children, in pregnancy and in breastfeeding mothers. Women who have received radioiodine should be also informed that they should not become pregnant within 4 months of treatment. The presence of Graves' ophthalmopathy and the use of radioiodine remains a contentious issue. There are data to suggest that administration of radioiodine to patients with 'unstable or progressive' thyroid eye disease may result in deterioration in ophthalmopathy.[46,47] Our practice is to maintain such patients on a thionamide, avoiding swings in thyroid function, and involving an ophthalmic surgeon at an early stage in shared care. Once the ophthalmologists report that the eye disease has remained stable for 18 to 24 months, we prescribe radioiodine. In the presence of Graves' disease that is very difficult to control with drugs alone and ophthalmopathy, we administer radioiodine under corticosteroid cover, since some evidence (including a recent study[47]) suggests that corticosteroid treatment reduces the risk of deterioration of thyroid eye disease.[48-50] Our steroid regimen involves starting prednisolone 40mg on the day of administration of

radioiodine, 30 mg/day for the next 2 weeks and a reducing dose thereafter, tailing off after 2 months.

5.2 Practicalities of Administration of Radioiodine

Prescribing and administration of radioiodine to patients must be undertaken by an authorised individual who holds a licence for such activities. In the UK, the physician must be accredited by the Administration of Radioactive Substances Advisory Committee (ARSAC) and patient and doctor are required to sign a consent form. Patients should receive literature relating to the consequences of radioiodine treatment, the importance of avoiding prolonged close contact (e.g. sharing a bed, prolonged nursing) with children, the necessity for time off work, avoidance of pregnancy within 4 months of treatment and the necessity and relevance of continued surveillance following the treatment. Patients can be reassured that there is no excess risk of secondary malignancies following treatment with radioiodine.[51-54] As pregnancy is an absolute contraindication to radioiodine treatment, it should be administered within 10 days of the onset of a menstrual period or after a negative pregnancy test.

5.3 Dosage and Outcome

The goal for the use of radioiodine should be to administer enough radiation to achieve euthyroidism without causing the patient to become hypothyroid. There appears to be much individual variability, however, in response to treatment with radioiodine. The practical compromise, therefore, is to administer a dose of radioiodine that achieves euthyroidism in most patients within 2 or 3 months, with a moderate rate of hypothyroidism thereafter – for example, 15 to 20% after 2 years and 1 to 3% annually subsequently.[55,56] There is no evidence that giving a calculated dose of radioiodine has any advantage over fixed doses of 200 or 400 MBq.[57] In patients with toxic nodular goitres or who within the past 4 weeks have received thionamides, we administer radioiodine 400 MBq as an initial dose. Patients who remain hyperthyroid 6 months after radioiodine therapy are administered a higher dose, in increments of 200 MBq. Other centres adopt other regimens. Larger initial doses of radioiodine may be used, especially in the context of an elderly patient with complicated hyperthyroidism.

If the patient has moderate to severe hyperthyroidism and/or requires large doses of thionamides to maintain a euthyroid state, continuing therapy with thionamides is prescribed 5 days after the administration of radioiodine. The dose prescribed is approximately equal to that which the patient was receiving before the radioiodine. Patients are initially assessed 4 weeks after radioiodine administration to detect the possibility of early hypothyroidism and subsequently every 6 weeks. Once the patient is euthyroid, any thionamide is discontinued and the thyroid function checked 6 weeks later. Once euthyroidism has been achieved, hyperthyroidism rarely recurs.[58,59] If the patient remains hyperthyroid 4 to 6 months after radioiodine therapy, another, larger dose (as described above) is prescribed. In the presence of hypothyroidism, any thionamide is discontinued but if the hypothyroidism continues (it can be temporary in the first 6 months after radioiodine therapy),[60] the patient is started on thyroxine therapy in conventional doses. Due to the 2 to 3% annual incidence of the development of hypothyroidism following radioiodine, long term follow-up is essential.

As an alternative to the method of radioiodine application mentioned above, some physicians are prepared to administer an initial large dose of radioiodine with a view to inducing permanent hypothyroidism in the majority and committing the patient to life-long thyroxine therapy.[61] The disadvantage of such an approach is ‘guaranteed’ radioiodine-induced hypothyroidism and the associated risks of excess or deficient thyroxine replacement therapy.

6. Surgery

In the hands of an experienced surgeon at a centre with a large throughput of patients, thyroid sur-

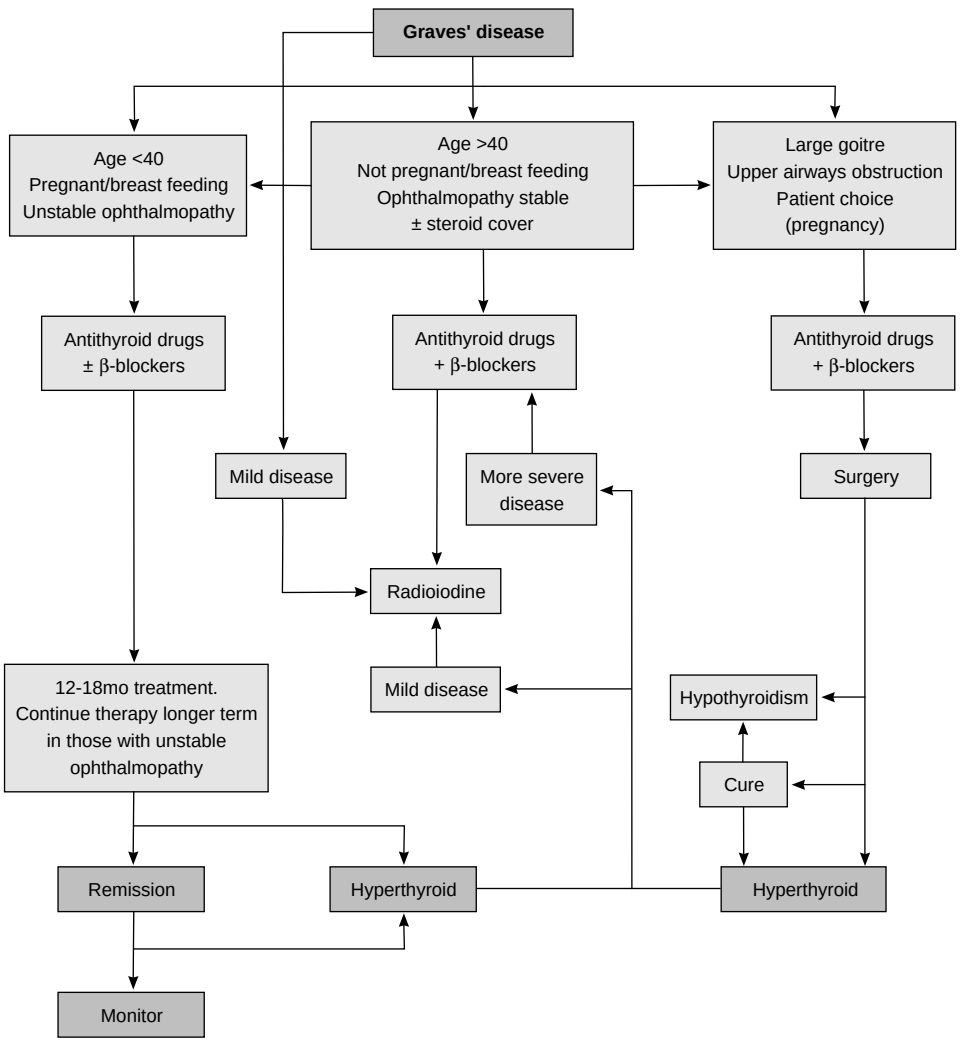

Fig. 1. A possible treatment strategy for Graves' disease.

gery is very safe. We rarely use surgery to treat patients with Graves' disease unless radioiodine is refused or there is a large goitre causing symptoms of compression in the neck. The goal of therapy is to cure the underlying pathology while leaving residual thyroid tissue to maintain postoperative euthyroidism. There are 2 operative procedures that may be performed, subtotal or near-total thyroidectomy. The objective is to cure the cause of the hyperthyroidism at first operation and not to have to re-explore the neck – a procedure associated with considerable morbidity. The major indications for surgery are large goitre, failed medical treatment due to noncompliance or adverse effects with thionamide drugs and patient preference. Surgery is a treatment option for Graves' disease in pregnancy, and should preferably be performed in the second trimester.

The pathology determines the long term success of surgery. Operations for solitary toxic adenoma

are highly successful and the anticipated outcome is euthyroidism. As a treatment for Graves' disease, results are not so good – at 1 year after surgery, approximately 80% of patients are euthyroid but permanent hypothyroidism occurs in 5 to 40% of patients and the prevalence increases with time.[55] Recurrent hyperthyroidism occurs in 1 to 3% of patients in the first year, thereafter occurring at 1% per year.[62,63]

Patients should be rendered euthyroid prior to thyroid surgery by the use of thionamide therapy as indicated above. The use of β-blockers alone is not adequate preparation. The specific complications of thyroid surgery are damage to the recurrent laryngeal and the external branch of the superior laryngeal nerves in 1 to 2% of cases,[64-66] and transient (up to 20%) and permanent (0 to 8%) hypocalcaemia.[64-67]

7. Treatment of Thyroid Storm

A thyroid storm represents the most severe expression of thyrotoxicosis and is characterised by fever, delirium, marked tachycardia, hypotension, vomiting and diarrhoea. It may be precipitated by induction of anaesthesia, surgery, systemic illness (particularly infection or sepsis) and radioiodine therapy.[43] The condition must be treated as a medical emergency with rapid institution of supportive measures including intravenous hydration, glucocorticoid therapy and large doses of PTU (100mg every 6 hours, which can be given via a nasogastric tube or rectally as necessary). PTU is the drug of preference because it also inhibits the peripheral conversion of T_4 to T_3. Potassium iodide (orally or intravenously) may also be administered to block the release of thyroid hormone but this should not be used as the sole treatment preoperatively (administration of potassium iodide without prior treatment with a thionamide may exacerbate hyperthyroidism). High dose β-blockade should also be instituted (propranolol 2 to 5mg every 4 hours intravenously or 320 to 480mg daily by mouth) to control heart rate.

8. Subclinical Hyperthyroidism

The entity of subclinical hyperthyroidism is defined as a persistently suppressed serum TSH concentration with normal T_4 and T_3 concentrations in a patient who does not have symptoms or signs of thyrotoxicosis. Long term follow-up of elderly patients with suppressed TSH concentrations has revealed a 3-fold relative risk of developing atrial fibrillation[68] and decreased bone density in postmenopausal women.[69] There is thus some evidence to suggest that such patients should be treated with radioiodine therapy, although this is not yet established practice.

9. Conclusions

Hyperthyroidism is a common problem that can be effectively treated via 3 distinct methods. Each mode of treatment has specific advantages and disadvantages but all suffer from the fact that none are 100% effective in offering a 'cure' while maintaining normal thyroid function following treatment. Figure 1 depicts an algorithm for decision-making in the treatment of hyperthyroidism due to Graves' disease, but as this article has indicated, there is much scope for individual 'fine-tuning' of such a treatment strategy.

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