Chapter

Treatment of Graves' Disease in Adults

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Abstract

Graves' Disease is an autoimmune disease, with a genetic susceptibility, activated by environmental factors like stress, iodine excess, infections, pregnancy and smoking. It is caused by thyroid stimulating immunoglobulin (TSI) or thyroid stimulating antibody (TSAb) and is the most common cause of hyperthyroidism with an incidence of 21 per 100,000 per year. Treatment of Graves' Disease includes antithyroid drugs such as methimazole and propylthiouracil, radioactive iodine therapy and thyroidectomy. Methimazole, an antithyroid drug that belongs to the thioamides class, is usually the first line of treatment due to lower risk of hepatotoxicity compared to propylthiouracil. Radioactive iodine therapy is reserved for those patients who do not respond to antithyroid drugs or have contraindication or adverse effects generated by antithyroid drugs, and thyroid surgery is an option in people with thyroid nodular disease with suspected malignancy or large goiters such as predictors of poor response to antithyroid drugs and radioactive iodine therapy. Multiple factors influence the management of patients with Graves' Disease including patient and physician preferences, access to medical services and patients features such as age, complications and comorbidities.

Keywords: Hyperthyroidism, Graves' Disease, antithyroid agents, methimazole, propylthiouracil, thyroidectomy

1. Introduction

Graves' Disease is the most common cause of hyperthyroidism with an incidence of 21 per 100,000 per year [1], with a F:M ratio ranging from 3 to 5:1 [2–4]. The usual age of presentation ranges from 20 to 50 years old.

Graves' Disease is an autoimmune disease, with a genetic susceptibility, activated by environmental factors like stress, iodine excess, infections, pregnancy and smoking. It is caused by thyroid stimulating immunoglobulin (TSI) or thyroid stimulating antibody (TSAb). TSI stimulate follicular thyroid cells by binding to the thyroid stimulating hormone (TSH) receptor on the thyroid cell membrane to produce the thyroid hormone synthesis and liberation as well as gland growth, with consequent hyperthyroidism and bocio [1, 5].

Graves' Disease produces varied symptoms such as sweating, insomnia, weight loss, anxiety, muscle weakness, loss of libido. Clinical signs include tachycardia, systolic hypertension, heart failure, atrial fibrillation, tremors, hyperkinesia, hyperreflexia, hot skin, palmar erythema, onycholysis, alopecia, goiter and impaired mental status. Among the most characteristic signs of the disease are thyroid orbitopathy and the infrequent pretibial myxedema. Orbitopathy is characterized by proptosis, palpebral retraction, chemosis, and periorbital edema [1, 5].

Treatment of Graves' Disease includes antithyroid drugs such as methimazole and propylthiuracil, radioactive iodine therapy and thyroidectomy. Methimazole, an antithyroid drug that belongs to thionamides class, usually is the first line of treatment due to lower risk of hepatotoxicity compared to propylthiuracil. Radioactive iodine therapy is reserved for those patients who do not respond to antithyroid drugs or have contraindication or adverse effects generated by antithyroid drugs, and thyroid surgery is an option in people with thyroid nodular disease with suspected malignancy or large goiters such as predictors of poor response to antithyroid drugs and radioactive iodine therapy [5–9].

Multiple factors influence the management of patients with Graves' Disease including patient and physician preferences, access to medical services and patients features such as age, complications and comorbidities.

2. Antithyroid drugs

2.1 Methimazole

Methimazole, an antithyroid drug that belongs to the thionamide class, with few exceptions is usually the first line of treatment due to the lower risk of hepatotoxicity compared to propylthiuracil [10, 11].

The mechanism of action of methimazole is to block the production of thyroid hormone by interfering with the iodination of tyrosine residues of thyroglobulin by inhibiting the enzyme thyroid peroxidase and then the synthesis of thyroxine and triiodothyronine. Furthermore, methimazole inhibits iodine oxidation and the binding of iodotyrosyl residues [10, 11].

The route of administration of methimazole is oral. The starting dose depends on the severity of the disease, in most cases it varies between 20 to 40 mg per day, with titration every 4 to 8 weeks and variable maintenance doses and a maximum dose of 60 to 80 mg. does not require dose adjustment except in patients with severe hepatic impairment [10, 11]. The recommended starting dose in mild cases is 15 mg per day and moderate to severe cases 30 mg per day.

Although methimazole has a half-life of less than 6 hours, the half-life has been shown to be greater than 6 hours in follicular cells [12, 13], and the effectiveness of administering it in a single daily dose in usual doses is effective [14–17].

In patients with thyroid storm, higher doses are required, with a starting dose of 60 to 80 mg per day with the dose divided every 4 to .8 hours, with a maximum dose of 120 mg [18].

Serious adverse effects of methimazole include agranulocytosis, hepatotoxicity, and teratogenicity. Agranulocytosis usually occurs in the first months of treatment but can occur at any time during treatment, it is characterized by an absolute granulocyte count less than 500 per ml, fever and sore throat, so it should be indicated to the patient attend the emergency room in case of these symptoms. Treatment consists of stopping methimazole if the granulocyte count is less than 1000 per ml and antibiotic treatment. Agranulocytosis due to methimazole predicts the risk of agranulocytosis due to propylthiuracil, therefore the use of propylthiuracil should also be avoided in these patients. Methimazole hepatotoxicity can occur at any dose, is characterized by cholestasis and slowly recovers after discontinuation of the drug [19–21].

The teratogenicity of methimazole occurs by free crossing the placenta, especially in the first trimester, the effects include aplasia cutis, umbilical malformations, facial dysmorphism, esophageal and choanal atresia as well as craniofacial malformations. For this reason, the use of propylthiuracil in the first trimester of pregnancy is preferred [19–21].

2.2 Propylthiuracil

Propylthiuracil is an antithyroid drug that is frequently used as a second treatment option in hyperthyroidism after methimazole due to an increased risk of hepatotoxicity, as well as in patients with a contraindication to methimazole or radioactive iodine therapy. Propylthiuracil is preferred as the first line of treatment in patients with thyroid storm because of its greater effect in theory, by inhibiting the peripheral conversion of t4 to t3 by inhibiting thyroid deiodinase. Propylthiuracil is also preferred in the first trimester of pregnancy because of the toxicity of methimazole [20, 21].

The mechanism of action of propylthiuracil is inhibition of thyroid peroxidase, which oxidizes iodine and incorporates it into the tyrosine molecule, preventing the formation of diiodotyrosine and monoiodothyronine. Unlike methimazole, it has a peripheral effect by inhibiting the conversion of T4 to T3 by inhibition of deiodinase [19, 20].

The route of administration is oral. The presentation is tablet of 50 mg. The initial dose depends on the severity with the usual starting dose 300 mg daily divided every 8 hours, with titration of the dose up to a maximum dose of 600 to 900 mg daily. The usual maintenance dose is 100 to 150 mg per day. In patients with thyroid storm the usual dose is 500 to 1000 mg daily divided every 4 hours [19–21].

Hepatic injury is one of the most worrisome adverse effects of the use of propylthiuracil, it occurs frequently in the first 6 months of treatment, however it can occur at any time, the symptoms are specific and the initial diagnosis is made by elevation of liver function markers. Due to the high risk of hepatotoxicity in pregnancy, methimazole is preferred in the second and third trimester of pregnancy [19–21].

Less frequently, propylthiuracil has been associated with ANCA-associated vasculitis that can cause glomerulonephritis, alveolar hemorrhage, central nervous system compromise, and leukocytoclastic vasculitis, may improve with drug withdrawal or require additional immunosuppressive treatment [19–21].

Agranulocytosis can occur in up to 0.5% of patients, especially in the first 3 months of treatment, the symptoms as in methimazole agranulocytosis are sore throat and fever and the patient should be advised of attend the emergency department in case of presenting these symptoms. Other adverse effects are hypersensitivity, hypothyroidism, and potential teratogenicity. Less frequently, multiple adverse effects have been described, including dermatological manifestations, interstitial nephritis, neuritis, paresthesia, headache, vertigo, lymphadenopathy, splenomegaly, aplastic anemia, fever, and lupus-like [19–21].

3. Initial treatment and relapse risk factors

Antithyroid drugs are the initial treatment for hyperthyroidism due to Graves' Disease, with the exception of patients who have contraindications. Methimazole is preferred as the first line of treatment due to a lower risk of liver toxicity and propylthiuracil as the second line of treatment, with the exceptions previously described [20, 21]. The relapse rate after initial antithyroid drug treatment based on a meta-analysis with more than 1000 patients is 52% [22].

There are factors that predict a higher remission rate with antithyroid drugs, some studies have identified factors such as female gender, not smoking, absence of orbitopathy, duration of treatment, pharmacological hypothyroidism, higher levels of TSH during treatment, more than 3 months of discontinuation of antithyroid drugs and lower levels of FT4 and FT3, antimitochondrial antibody level and

factors associated with a higher relapse rate such as antithyroid use for more than 24 months [23–25], Scores such as GREAT have also been created that give a higher relapse risk score to people under 40 years of age, with greater ft4 level, higher levels of Thyrotropin-binding Inhibitory Immunoglobulin (TBII), greater degree of goiter and HLA polymorphisms [26].

After 12 to 18 months of antithyroid treatment, the patient should be reassessed and depending on the risk factors for relapse as well as the TRBII titers, continuing treatment with antithyroid drugs for an additional 12 months or taking the patient to therapy may be considered. Ablative with iodine 131 or surgery, depending on the age, comorbidities and desire of the patient, taking into account risks and benefits of each therapy. In selected patients, one option is to continue treatment with antithyroid drugs. In patients seeking pregnancy or pregnancy who are being treated with methimazole, it is recommended to switch to propylthiuracil during the first trimester of pregnancy [27].

The use of combined therapy with methimazole and levothyroxine has been evaluated in some studies, however it has been found that it does not increase the rate of remission of the disease with the probability of increasing adverse effects [28, 29], with the exception of one study which demonstrated a probable benefit in bone mineralization with the use of combination therapy [30].

3.1 Beta blockers

Beta-blockers are an adjuvant to antithyroid drugs, radioactive iodine, or surgery. They have been used for more than 20 years to modify the severity of general symptoms due to excess thyroid hormones by blocking the hyperadrenergic effects. The effects of the different beta-blockers depend on their selectivity for B1 receptors, membrane stabilizing activity, sympathomimetic activity, and lipid solubility [31–33].

Some beta-blockers such as propranolol have effects on the metabolism of thyroid hormones by decreasing the conversion of T4 to T3, decreasing the levels of active hormone T3, this effect is not typical of all beta-blockers and has been associated with the stabilization activity of membrane [31–33].

When comparing treatment with propranolol and metoprolol, it has been shown that both are equally effective in controlling the symptoms and signs of thyrotoxicosis, however propranolol produces a decrease in T3 and an increase in reverse rT3 by the mechanism previously described, findings that are not known. Found in patients treated with metoprolol [31–33].

In conclusion, beta-blockers are effective in treating the metabolic and hyperadrenergic symptoms of hyperthyroid states and in the case of Graves' Disease they are an adjuvant treatment to antithyroid drugs and ablative therapies [31–33].

3.2 Iodine 131 (I131) therapy

Ablative treatment with radioiodine or thyroidectomy result in better cure rates and overcome the risk of non-compliance with thionamides, but both treatments incur the need for permanent levothyroxine therapy [34].

The mechanism of action of I131 is physiological, it is taken up by the thyroid gland and incorporated into thyroid hormone, releasing beta particles that cause ionizing damage and tissue necrosis, this results in ablation of functional thyroid tissue. On average, it takes between 6 to 18 weeks before an euthyroid or hypothyroid state is achieved following I131 treatment. After a single dose of radioiodine, around 15–25% of patients remain hyperthyroid and require additional treatment [35].

Iodine therapy represents a cost-effective treatment option for Graves' Disease. In the United States is the preferred therapy, whereas in Europe, Australia and most of Asia, it is reserved as second line for patients who relapse after initial thionamide treatment [34, 36]. The recent National Institute for Health and Care Excellence (NICE) guidelines recommends that radioiodine should now be the first line treatment for Graves' Disease in the UK because of its superior cost-effectiveness and efficacy of radioiodine compared to thionamides [34].

Previous studies have reported factors related to success of radioiodine therapy (RIT) including: gender (lower remission rates in males), more severe hyperthyroidism, thyroid size, serum TSH receptor antibody titers and thyroid uptake on radionuclide scans [36]. A recent study included 336 patients aged 22–75 years who were diagnosed with Graves' Disease and treated with iodine therapy, which 220 (65.5%) were smokers. In regards of the treatment, 115 (52.2%) of patients received single RIT and 105 (47.8%) received second dose of RAI due to recurrent hyperthyroidism. In non-smokers (n = 116, 34.5%), 91 (78.6%) received single activity of RAI, while 25 (21.4%) required second RIT due to recurrent hyperthyroidism [36].

Potential complications of I131 therapy include: worsening of Graves' ophthalmopathy (15–20% of patients) and development of a radiation thyroiditis (1% of patients), which appears within 2 weeks after I131 therapy and can be associated with neck tenderness and swelling. The risk of exacerbation or new occurrence of Graves' eye disease can be mitigated by glucocorticoid prophylaxis [35, 36].

Regarding outcomes of radioiodine therapy, data from 101 patients in an Australian 10 year cohort reported remission following a single dose of I131 in 73 patients (79.3%), 64 patients became hypothyroid (87.6%) and 9 patients (12.3%) remained euthyroid. Individuals who did not achieve remission with a single dose were more likely to have higher TSH receptor antibody titers at diagnosis. The median time from I131 administration to hypothyroidism was 4 months. There was no difference in technetium uptake, I131 administered activity, duration of medical therapy, pre-treatment free thyroxine or duration of disease [35].

The safety of radioiodine with respect to long-term mortality risk has been subject of debate; observational studies from the United States, Sweden, UK and Finland reported increased all-cause mortality compared to the background general population in patients who received radioiodine therapy for hyperthyroidism, attributable to cardiovascular disorders, and in some cases, mortality increased with higher radioiodine doses. Along cancer mortality, there are reports of increased, similar or decreased cancer mortality risk in radioiodine-treated patients with hyperthyroidism. The increased mortality was seen in younger versus older patients, and in patients with toxic nodules compared to Graves' Disease. Mortality cancer risk was dose dependent, and it attributable to upper gastroesophageal, respiratory tract or breast tumors, suggesting that the malignancies were a consequence of internal exposure to radioactivity in iodide accumulating organs. A critical appraisal of these and other treatment-related mortality studies in hyperthyroidism is therefore necessary to ascertain the safety of the proposed NICE approach [34].

There are several studies that compare mortality in radioiodine versus thionamide treated patients. Some showed excess cancer deaths in thionamide but not radioiodine-treated patients, and others showed reduced mortality in association with radioiodine but only after it led to hypothyroidism, implying survival advantages of hyperthyroidism control [34].

3.3 Surgery

Thyroidectomy is the oldest form of Graves' treatment and has been found to be as effective as ATDs and radioiodine in normalizing serum thyroid hormone

levels within 6 weeks of therapy. A meta-analysis that included 8 studies and a total of 1402 patients with hyperthyroidism has shown that thyroidectomy has the lowest relapse rate (10%) when compared with RAI (15%) and ATD (52%) as well as another meta-analysis which showed a 100% cure rate among patients who underwent total thyroidectomy [37].

Indications for thyroidectomy include large goiters, goiters causing airway obstruction/ dysphagia, moderate to severe ophthalmopathy (because radioiodine may worsen ophthalmopathy), pregnant or breastfeeding women (If the patient is unable to tolerate propylthiuracil or methimazole after the first trimester, persistent hyperthyroidism after radioablation and ATD therapy, or a nodule with abnormal cytology on fine needle aspiration (FNA) [37].

Regards of mortality outcomes in radioiodine versus thyroidectomy cohorts. A 1982 Mayo clinic study showed no difference of mortality in radioiodine versus surgically treated women with hyperthyroidism, but two studies from Finland and Sweden have shown an increase in all-cause mortality and cardiovascular mortality in radioiodine treated patients compared to thyroidectomy patients; differences in cancer related mortality were not observed between the two groups in these cohort. Excess cardiovascular morbidity was not seen in radioiodine or in surgically who developed hypothyroidism, suggesting that the survival advantages of surgery over radioiodine therapy may be related to the superior hyperthyroidism control achieved with thyroidectomy [34].

Preparing for surgery [37]:

- Thyrotoxic patients should be rendered euthyroidic before undergoing surgery, some believe that there is a risk of hemodynamic instability if thyroid function is not controlled

- Beta blockers should be used up to and after surgery until thyroid function levels are within the normal limits

- Antithyroid drug therapy is used up until the day of surgery

- According to ATA guidelines, preoperative potassium iodide (KI), saturated solution of potassium iodide (SSKI), or Lugol solution should be used, this treatment has been shown to decrease thyroid blood flow, vascularity, and intraoperative blood loss. Although, there have also been other studies that show no change in outcomes when using these products.

- Calcium and vitamin D levels should be measured prior to surgery to establish a baseline level

- Serum calcium and albumin levels should be measured in the postoperative setting

- Parathyroid hormone is tested postoperatively after thyroidectomy to screen for transient and later permanent hypoparathyroidism

- Postoperative hypocalcemia can be avoided by pretreating with calcium carbonate 1 g for 3 weeks prior the procedure

- All patients should take 1 g calcium carbonate TID for 2 weeks until the levels of calcium and parathyroid hormone (PTH) are measured again

Total thyroidectomy is preferred to subtotal thyroidectomy. Total thyroidectomy versus subtotal thyroidectomy is a balance between risk of recurrence of hyperthyroidism and incidence of hypothyroidism [37].

One randomized trial of total thyroidectomy vs. subtotal thyroidectomy followed 191 patients over a span of 5 years. Total thyroidectomy had a recurrence of 0% versus 4.7% in patients undergoing subtotal thyroidectomy. It was also found that transient hypoparathyroidism occurred in 12.6% of total thyroidectomy and permanent hypoparathyroidism in 0.5% patients. In the subtotal thyroidectomy cohort, 6.8% had transient hypoparathyroidism and 0% had permanent hypoparathyroidism [38].

A systematic review and meta-analysis of total vs. subtotal thyroidectomy for Graves' Disease, found that the odds ratio (OR) of transient and permanent hypoparathyroidism favors subtotal thyroidectomy, the OR of the recurrence of hyperthyroidism favors total thyroidectomy. Permanent recurrent laryngeal nerve injury was found to be equivalent between the 2 operations [39].

3.4 Thyroid storm

Thyroid storm is a life-threatening complication of severe disease with a high risk of mortality. Once thyroid storm is recognized, the patient should be managed in an appropriate location such as an Acute Medical Unit, high-dependency area or intensive care unit [40, 41].

Thyroid storm has multiple aims: supportive care, inhibition of new hormone synthesis, inhibition of thyroid hormone release, peripheral β-adrenergic receptor blockade, preventing peripheral conversion of T4 to T3 and identifying and treating precipitating factors [41].

General supportive care includes intravenous resuscitation, electrolyte replacement and nutritional support. Fluid losses could result from the combination of fever, diaphoresis, vomiting, and diarrhea. Normal saline can be given for replacement [40, 41]. Antipyretics can be administered to relieve pyrexia, but salicylates should be avoided as they are associated with displacement of thyroid hormone binding from thyroid binding globulin [40].

Thionamides inhibit synthesis of thyroid hormones. Iodine (lugol solution, potassium iodide can be given to stop thyroid hormone release. Iodine-containing solution should not be given to patients with iodine overload, iodine-induced hyperthyroidism, or those with amiodarone-induced thyrotoxicosis. In these situations, an alternative such as lithium or potassium perchlorate may be used instead [41].

Conversion of T4 to T3 is blocked by PTU, propranolol, and glucocorticoid. For PTU and propranolol, this effect is not quantitatively significant. Therefore, glucocorticoids like hydrocortisone or dexamethasone are essential in treatment [41].

Peripheral β-adrenergic receptor blockade is made by using propranolol. It can be given intravenous in slow 1–2 mg boluses, which may be repeated every 10–15 min until the desired effect is achieved. Orally, propranolol therapy usually begins at 20–120 mg per dose, or 160–320 mg/day [41].

Propranolol could be used for the management for secondary atrial fibrillation. Alternatively, esmolol, with a shorter acting effect could also be used. Intravenous calcium channel blockers may be considered if β-blockers are contraindicated, other alternatives are digoxin and amiodarone [41].

The incidence of thromboembolism in thyrotoxic patients is considerable. In view of the hypercoagulable state and increased incidence of mitral valve prolapse in thyrotoxicosis-related atrial fibrillation, anticoagulant should be started [41].

In the case of acute heart failure, which is associated with a high cardiac output state, initial management is with loop diuretics. Vasodilators such as nitrates should be avoided as thyrotoxicosis is associated with vasodilatation and systemic vascular resistance [41].

4. Future therapies

Although antithyroid drugs, radioactive iodine and surgery have been the treatment options in the las few decades, in recent years treatment options based on immunobiology such as biologics, small molecules and peptide immunomodulation have been investigated. These treatments are in different stages of development and are aimed at immunomodulation of B lymphocytes such as rituximab, iscalimab and belimumab, blocking of immunoglobulin recycling, signaling of TSH receptors as antagonists of TSH receptor, immune tolerance as immunomodulatory TSH receptor peptides, with the benefit of a lower risk of toxicity and since they are targeted treatments, a lower risk of immunosuppression and the hope of higher rates of remission [42].

5. Conclusions

Graves' Disease is the most common cause of hyperthyroidism. Treatment options are still antithyroid drugs, radioactive iodine and surgery. Antithyroid drugs continue to be the first line of treatment, except for patients with contraindications or intolerance, radioactive iodine therapy has gained more force in some management guidelines such as the NICE 2019 guidelines. Surgical ablation is still an option in a smaller proportion of patients with particular conditions. New treatment options with biological and immunomodulatory therapy are under development and in the future may be a treatment option with a lower risk of toxicity and perhaps higher rates of cure.

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