**Indefinite antithyroid drug therapy in toxic Graves’ disease: What are the cons**

**Rajesh Rajput, Vasudha Goel**  
Departments of Medicine VI and Endocrinology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

**ABSTRACT**  
Existing treatment modalities for Graves’ disease includes antithyroid drugs (ATDs), radioactive iodine, and surgery. There has been a lack of general agreement as to which therapy is the best as none is ideal since all effectively restore euthyroidism, but with some limitations. Previously, therapies were selected with the goal of achieving euthyroidism. Instead, hypothyroidism is now the goal of treatment, to ensure that hyperthyroidism does not recur. Current evidences suggest that high relapse rate and not so rare fatal side effects seen with ATD therapy compel one to consider other definite modes of treatment like radiotherapy and surgery for toxic Graves’ disease after discussing this with the patient.

**Key words:** Antithyroid drugs, definitive therapy, graves’ disease

**INTRODUCTION**

Graves’ disease is the most common cause of spontaneous hyperthyroidism in patients younger than 40 years of age and represents 50-80% of all cases of thyrotoxicosis. It is an autoimmune disorder caused by stimulating antibodies like thyroid stimulating immunoglobulin (TSI) which bind to and activate thyrotropin receptor on thyroid cells, thus not only inducing the synthesis and secretion of thyroid hormone but also hypertrophy and hyperplasia of thyroid follicles. Prevalence in men was one-fifth to one-tenth of that in women. The prevalence of Graves’ disease was found to be similar among Whites and Asians. Susceptibility to Graves’ disease is determined by a mixture of genetic, endogenous, and environmental factors like female sex, stress, smoking, iodine supplementation, etc.

**TREATMENT**

Existing treatment modalities for Graves’ disease includes antithyroid drugs (ATDs), radioactive iodine, and surgery. There has been a lack of general agreement as to which therapy is the best as none is ideal since all effectively restore euthyroidism, but with some limitations. Thus, patients should be well-informed about the available treatment options, their potential side effects, and be a part of the decision regarding the choice of therapy. There is also regional variation in the use of appropriate therapy. Radioiodine (RAI) is favored in North America and ATD therapy in Europe and Japan.

The goals of treatment in Graves’ disease have been an efficient control of symptoms, restoration of euthyroidism, with least adverse effects, and at the same time ensuring cost-effectiveness. Most treated patients in Graves’ disease eventually go on to develop hypothyroidism regardless of the treatment modality used. This awareness of inevitable hypothyroidism with Graves’ disease has led to a change in the objective of treatment. Previously, therapies were selected with the goal of achieving euthyroidism. Instead, hypothyroidism is now the goal of treatment, to ensure that hyperthyroidism does not recur.
The ATDs used belonged to thionamide class and includes methimazole (MMI), carbimazole, and propylthiouracil (PTU). Drug selection is largely determined by local practice. For instance, PTU is the drug of choice in North America, carbimazole in the United Kingdom, and MMI elsewhere in Europe and in Asia. Maximum clinical response occurs after a latent period of 4-6 weeks and ATD therapy should be continued for a period of 12-18 months after achieving euthyroidism. A major clinical drawback of ATD therapy is the high rate of relapse seen after discontinuation of therapy. Irrespective of the treatment duration, the best long-term remission rate achieved with the use of these drugs alone is about 40-50%. These rates are even lower in children’s, men, older patients, smokers, those with large goiters, and more active disease. Prolonged drug therapy has not been shown to increase the likelihood of lasting remission. No difference in remission rates have been seen in subjects treated with for 24 versus 12 months or 42 versus 18 months. Weetman reviewed prospective trials comparing different duration of treatment and showed that remission rates are not improved with ATD therapy beyond 18 months in adults. Particular attention has been paid to refining treatment options in pediatric Graves’ because of the recognition of the fact that remission occurs in only a minority of individuals. An extensive study involving nearly 200 children showed that less than 20% of the children treated medically achieved remission lasting more than 2 years. In another large series involving 186 children, less than 30% went into remission. In cases of relapse with an ATD, there is little chance that a second course of treatment will result in permanent remission. High recurrence rate seen with ATD therapy necessitates prolonged ATD therapy, which decreases the cost-effectiveness of therapy because of the need of repeated clinic visits, thyroid function testing, and cost of drug. These factors promote poor drug compliance, especially in children who need prolonged ATD therapy. Recurrent untreated hyperthyroidism causes deterioration in the quality of life and may increase morbidity particularly in the elderly who are at risk for conditions like atrial fibrillation. Hence, need arises of more definitive treatment modalities for toxic Graves’ disease that are focused on “cure” of the disease and create a stable situation earlier in the course of therapy. Not only this, use of ATD therapy has been associated with various side effects. Mild side effects, occurring in 20% of the patients, include: Skin reactions, arthralgias, gastrointestinal symptoms, abnormal sense of taste, and occasional sialadenitis. The serious side effects include agranulocytosis, fulminant hepatic necrosis, and antineutrophil cytoplasmic antibody (ANCA) positive vasculitis; and these can happen anytime during the course of therapy. Agranulocytosis occurs in 0.1-0.3% of patients and elderly patients and those at higher doses are at higher risk. Discontinuation of therapy is needed if symptoms such as fever, sore throat or mouth ulcers should develop or absolute neutrophil count falls to less than 1,500 cell/μL. PTU has been associated with fulminant hepatic necrosis and is the third most common cause of drug related liver failure, accounting for 10% of the entire drug related liver transplantsations. The hepatotoxic drug effect can continue despite drug discontinuation and can be fatal. Over a period of 20 years in US, 22 cases of PTU related liver failure in adults have been reported (including nine deaths and five liver transplantsations), while 12 children developed liver failure (including three deaths and six transplants). On the basis of these findings it was estimated that 1 in 10,000 adults taking PTU and 1 in 2,000 children taking PTU are at risk of this life-threatening complication. Therapy with PTU, which up to 10 years ago, was commonly used in pediatric Graves’ is now discouraged in children. Vasculitis positive for ANCA has also been reported as a rare complication of PTU use. MMI is associated with cholestasis rather than hepatic necrosis. Steven-Johnson syndrome is another life-threatening complication observed with MMI use in children. Many times hyperthyroid subjects taking ATDs conceive and then issue of teratogenicity with the use of ATDs during pregnancy comes. MMI has been associated with aplasia cutis, a localized defect of the skin on the vertex of the scalp and with other congenital anomalies such as esophageal and choanal atresia. PTU is therefore preferred over MMI or carbimazole during pregnancy. High doses of PTU in pregnant women, on the other hand expose the fetus to the risk of fetal hypothyroidism.

RAI has been commonly used for the treatment of hyperthyroidism and it has been considered effective, safe, and inexpensive. The aim of therapy is to treat hyperthyroidism by destroying sufficient thyroid tissue so as to render the patient euthyroid or hypothyroid. I131 is a β-emitting radionuclide with an average energy of 0.192 MeV and is the radionuclide of choice because of its long half-life of just over 8 days. I131 is administered orally in solution or as a capsule and is absorbed rapidly; after which it is concentrated, oxidized, and organified by thyroid follicular cells. It destroys thyroid cells by an early inflammatory response and necrosis of follicular cells. Subsequently, chronic inflammation and fibrosis result in a decrease in thyroid size and an impaired ability to secrete thyroid hormones. Following I131 therapy, thyroid secretion declines gradually over weeks to months and the time taken to achieve euthyroidism is usually 6-8 weeks. During this period, symptoms can be controlled with a β-adrenergic antagonist or if necessary an ATD. With RAI 80-90% of patients ultimately become euthyroid or hypothyroid after a single fixed dose of 10-15 mCi (370-555 MBq) range. RAI use has been described not only in adults, but also
in children and adolescents. Rivkees et al., have detailed the use of RAI in more than 1,200 children. Patients as young as 1 year of age have been treated with $^{131}$I with excellent outcomes. Studies have reported remission rates that exceed 95%, with very rare complications. Several studies have shown that treatment with $^{131}$I is more effective in achieving euthyroidism as compared with ATDs (relative risk (RR), 1.70; 95% confidence interval (CI), 1.29-2.24) in pediatric patients with Graves’ disease. Recently published Brazilian consensus statement on diagnosis and treatment of hyperthyroidism in 2013 clearly recommends that treatment with $^{131}$I should be avoided in only children younger than 5 years of age, however in older children, radioactive iodine dosing is an effective and safe therapy and can be performed using fixed or calculated doses.

The main sequel of radioactive iodine therapy is hypothyroidism. Since hypothyroidism is also the goal of treatment of hyperthyroidism; to ensure that hyperthyroidism does not recur, the issue of hypothyroidism does not deter one to use RAI as therapeutic option for treatment of hyperthyroidism. There is a positive relation between $^{131}$I dose and the development of hypothyroidism within the 1st year of therapy. On the other hand, the incidence of hypothyroidism beyond 1 year due to lymphocytic infiltration and tissue destruction seems to be largely independent on $^{131}$I dose and is around 2-3% annually. Thus, higher doses of RAI are favorable in order to permanently cure hyperthyroidism. Few acute adverse responses to $^{131}$I therapy of Graves’ disease have been described. Transient nausea and radiation thyroiditis with pain over the thyroid gland have been described in 1% of adult patients after 5-10 days. These side effects are self-limited and respond to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). RAI therapy can worsen Graves’ ophthalmopathy, particularly in smokers. When profound Graves’ ophthalmopathy is present, adjunctive prednisone therapy for 3 months has been shown to prevent the worsening of eye disease after RAI.

RAI therapy has no significant adverse effects on fertility rates or on the offspring of children and adolescents who have been treated with RAI. Literature contains data on 500 offsprings born to approximately 370 subjects treated with $^{131}$I for hyperthyroidism during childhood and adolescence. The incidence of congenital anomalies reported among the offspring of patients treated with RAI does not differ from the incidence in the general population. There has been no established teratogenic risk of RAI. However, due to transplacental passage and passage into breast milk, pregnancy, and breastfeeding are absolute contraindications to $^{131}$I therapy. Pregnancy should be avoided during the first 4-6 months after $^{131}$I therapy.

The thyroid gland is unique in its developmental sensitivity to malignancy after radiation exposure. There has been concern over increased rates of thyroid cancer and thyroid nodules observed in young children exposed to radiation from nuclear fallout at Hiroshima or after the Chernobyl nuclear reactor explosion. However, such data are not applicable when assessing risks for $^{131}$I therapy. The risk of thyroid neoplasms is greatest with exposure to low level external radiation, not with the higher doses used to treat Graves’ disease. The Cooperative Thyrotoxicosis Therapy Follow-up Study also showed that thyroid neoplasms developed in children treated with lower rather than higher doses of RAI.

Residual thyroid tissue left after suboptimal doses of radiation increases a theoretical risk of thyroid cancer. No increased risk of thyroid malignancy was revealed after high dose $^{131}$I treatment of Graves’ disease in more than 1,200 children and adolescents. The duration of follow-up in these studies ranged from less than 5 year to 15 year, with some subjects followed for more than 20 year. Read et al., surveyed more than 100 children for nearly 4 decades after receiving radioactive iodine, and reported no adverse events or deaths attributable to $^{131}$I therapy. Radioactive iodine therapy is avoided in children less than 5 years of age as risks of thyroid cancer after external irradiation were observed to be highest in children younger than 5 year of age and progressively decline with advancing age. ATDs are preferred to radioactive iodine therapy by some clinicians, assuming that thyroid cancer risk is less after drug therapy than after radioactive iodine. The cooperative thyrotoxicosis therapy follow-up study compared the incidence of thyroid carcinomas with the three treatment modalities after a follow-up of 10-20 years. The incidence of thyroid carcinomas was found to be five-fold higher in individuals treated with thioamide drugs than in patients treated with $^{131}$I, and eight-fold higher than in patients treated surgically.

Several authors have established cost-effectiveness of RAI therapy over ATD therapy. Qari et al., observed a significant cost benefit of treating patients with radioactive iodine, and proved this modality to be the most cost-effective in Saudi Arabia. Cost of medical treatment was eight times as expensive. A group from Germany, using costing models that included follow-up care for 30 years, showed RAI to be a cost-effective first line therapy in patients with a special risk of relapse after primary conservative therapy.

Thyroid surgery is a definitive treatment option that may be used particularly as an alternative to radioactive iodine during recurrent hyperthyroidism or in uncontrolled hyperthyroidism despite high doses of ATDs. This may also be considered during poorly controlled hyperthyroidism
dysfunction during pregnancy or if there is a suspicion of a coexistent malignant thyroid nodule. Patients with large goiters particularly with compressive symptoms, with poor compliance with ATDs, or with severe ophthalmopathy would also be suitable candidates for a surgical approach. Most surgeons now recommend total or nearly total thyroidectomy rather than subtotal thyroidectomy leaving a few grams of each lobe. A meta-analysis found that thyroidectomy cures hyperthyroidism in more than 90% of cases. Operative mortality these days is rare. However, thyroidectomy is complicated by recurrent laryngeal nerve injury or permanent hypoparathyroidism in 1-2% of patients. Transient hypocalcemia, bleeding, or infections are also potential complications. It results in permanent hypothyroidism in most patients. Surgery is also more costly than therapy with an ATD or radioactive iodine.

Recently Sundaresh et al., compared effectiveness of therapies for Graves’ hyperthyroidism in eight studies with 1,402 patients from five continents. Mean follow-up was 57, 64, and 59 months for ATDs, RAI, and surgery, respectively. Network meta-analysis suggested higher relapse rates with ATDs (52.7%, 352/667) than radioactive iodine (15%, 46/304) (odds ratio [OR] 6.25; 95% CI: 2.40-16.67) and with ATDs than surgery (10%, 39/387) (OR 9.09; 95% CI: 4.65-19.23). There was no significant difference in relapse between RAI and surgery. Examination of 31 cohort studies identified adverse effects of ATDs in 692/5,136 (13%) patients. These were more common with MMI, mainly owing to dermatologic complications, while hepatic effects were more common with PTU use. This study concluded that ATDs are associated with relatively high relapse rate in comparison to RAI or surgery, along with a significant side effect profile for these drugs and the current data can help in having informed discussion between physician and patients regarding choice of therapy for Graves’ disease.

To conclude with, we have ample data that addresses the concerns of various treatment modalities in Graves’ disease. In conclusion, the high relapse rate and not so rare fatal side effects seen with ATD therapy compel us to consider other definite modes of treatment for toxic Graves’ disease.

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