MEDICAL TREATMENTS FOR GRAVES' AND HYPERTHYROIDISM

Available Conventional Treatment Options

By Elaine Moore

Conventional and alternative medicine have identical primary goals when it comes to treating Graves’ disease (GD). Both medical and alternative treatment options attempt to reduce the amount of thyroid hormone available in the blood. However, alternative treatments also address the underlying causes. Because of their subtle action, alternative options are best reserved for patients with mild symptoms. Conventional options for GD, although more aggressive, are usually necessary for managing patients with moderate to severe symptoms.

Reducing Symptoms

Conventional medicine rapidly reduces certain overt symptoms, which, if left untreated, could lead to severe complications, including thyroid storm. However, conventional treatment doesn’t address the underlying causes. Also, both surgery and radioiodine ablation (RAI) cause hypothyroidism in more than 50% of treated patients. Spontaneous remission in GD (without treatment) occurs at a rate of 10% to 25% each year. And most GD patients eventually become hypothyroid spontaneously. These factors should be considered before deciding on treatment.

Conventional medicine offers three major options for treating GD: 1) the medical administration of antithyroid drugs (ATD’s) which inhibit thyroid hormone synthesis, 2) partial or complete surgical removal of the thyroid gland, and 3) radioiodine ablation. The latter two options limit the amount of functional thyroid tissue capable of producing thyroid hormone. In this article I describe these treatment options along with another viable option, the use of ionic inhibitors. In addition, I describe beta adrenergic antagonists, a class of drugs often prescribed to manage symptoms of hyperthyroidism.

In the current (1998) edition of Williams’ Textbook of Clinical Endocrinology, Larsen, et al recommend that several considerations be taken into account when deciding on treatment, including age, sex, general health, thyroid status, personal philosophy, and the preference of the physician based on his or her experience. Larsen, et al recommend that all patients use ATDs for at least 18 months before deciding on a permanent course of action.

Antithyroid Drugs

Antithyroid drugs (ATDs) have been a mainstay in the management of Graves’ disease since their introduction in the mid-1940’s. ATDs are reported to be extremely (at least
90%) effective in controlling the symptoms of Graves’ disease. ATDs effectively inhibit thyroid hormone production. However, their effects aren’t immediate. The stores of thyroid hormone present in the thyroid must be used up before symptoms subside. After several weeks, when these hormone stores are depleted, effects become noticeable.

ATDs also have an immunosuppressive effect giving this option a conventional advantage since immunosuppression influences the disease course, slowing disease progression. The drug PTU also inhibits the peripheral conversion of T4 to T3.

In the United States two antithyroid drugs are available for treating Graves’ disease: Propylthiouracil (PTU) and Methimazole (1-methyl-2-mercaptopimidazole or MMI, Tapazole). In Europe, the Methimazole derivative Carbimazole is used. Since Carbimazole is rapidly metabolized to MMI, these drugs are essentially the same.

The choice of drugs depends on several factors. In pregnancy and in nursing mothers, PTU is preferred since it is less likely to cross the placental barrier and affect the fetus. If there are signs of fetal thyrotoxicosis, however, Methimazole is used since it can simultaneously treat fetal symptoms. PTU has been in use longer and is prescribed more often. Having a shorter half life (time when the initial concentration is reduced by 50%) of 75 minutes, it must be taken more frequently. The duration of action of PTU, however, is about 12 to 24 hours. At the onset of therapy, patients usually take PTU every 6 to 8 hours. The usual starting dose is 100 mg given 3 times daily.

Methimazole with its longer half life of 4-6 hours can be taken once daily. The starting dose is 20 to 30 mg. Patients on either ATD usually have a dosage change after 4-12 weeks. Methimazole causes euthyroidism quicker, taking four weeks, while PTU may take as long as 12 weeks. If there is no improvement, the dose is increased. With evidence that the drug is working (weight gain, reduction in goiter), the dosage is usually reduced.

Patients on Methimazole go into remission sooner than patients on PTU and are thought to have less trouble with side effects or eye complications. Although PTU is reported to be more expensive than Methimazole, several online patients have reported Methimazole as being significantly more expensive.

ATDs are used until patients go into spontaneous remission. Remission occurs as a result of the natural disease course although it may be amiablely affected by the immunosuppressive effects of ATDs. Older patients (reported to usually have milder disease) and patients with small goiters usually go into remission sooner. Although there are reports of patients achieving remission after several weeks, 50% of patients achieve remission within 4 years. Relapses are more likely in the postpartum period.

If large ATD doses continue to be required for control, remission is considered unlikely. Autoantibody levels may be required to confirm this since sustained high antibody titers are also seen in patients unlikely to achieve remission. In this case, an integrative approach employing craniosacral therapy, traditional Chinese medicine, acupuncture or
other energy healing methods may prove to be beneficial. Also, the adjunctive use of ionic inhibitors has shown benefits in patients who show resistance to ATDs.

Although patients in Europe are kept on ATDs as long as necessary until remission is achieved, many American doctors are hesitant to do so and recommend a more aggressive approach if remission isn’t achieved within 18 months. Cost containment is often a factor since patients on ATDs should be monitored closely every 2 to 4 weeks.

Side effects of both Methimazole and PTU are rare and include minor effects (seen in 1% to 5% of patients) such as rash, urticaria, arthralgia, fever and transient leukopenia (decreased white blood cell count). Rashes and hives should be reported to the doctor immediately. In most instances, treatment in the form of antihistamines is prescribed and the medication is continued.

There may also be rare gastrointestinal effects and rare (0.2% to 0.5%) major effects such as agranulocytosis where white cell levels become critically low. For this reason patients are advised to notify their doctor at the first sign of a sore throat or infection. At this time, a white blood cell count (WBC) is generally ordered. If the WBC count is critically low, the ATD is discontinued and appropriate antibiotics are prescribed. Other very rare side effects include aplastic anemia, thrombocytopenia (low platelet levels), and hypoglycemia. Hepatitis is a very rare effect and is seen only with PTU. Patients may be allergic to one of the ATDs, but patients are rarely allergic to both. PTU has also been recently listed in the same category as estrogen as a potential carcinogen. As with any treatment, however, the potential benefits must be weighed against potential risks.

**Block and Replace Protocol**

In the block and replace protocol, patients are kept on the usual starting doses of ATDs until they become euthyroid. Then, rather than decreasing the ATD dose, a low dose of thyroxine is added to the regimen. Patients following this protocol are thought to have more stable thyroid levels and they are less likely to become drug resistant. In the original studies of Yamamoto, thyroid function was assessed after one year by an RAI uptake scan. At uptake levels less than 25%, the drugs were weaned. This approach effectively predicted probable remission. With this protocol, remissions were reported to be achieved in more than 90% of patients.

In some Block and Replace protocols, the drugs are slowly weaned over time until patients remain on a low dose of levothyroxine alone. This helps to reduce glandular activity and diminish thyroid hormone production. Usually, patients are kept on a low dose of levothyroxine or Armour thyroid for 1 year or indefinitely if thyroid function appears stable.

**Imaging Studies**

Recent studies indicate that using ultrasonography as a tool to measure thyroid volume has the same predictive effect as using an uptake test to predict remission. Measuring
stimulating TSH receptor antibody titers and comparing them to baseline levels also works. Without routinely used guiding factors, the block and replace protocol as used in the U.S. has met with limited success.

**Using the TSH Level to predict remission**

Studies show that the TSH level can also be used to predict remission. Because TSH levels falsely lower TSH levels, a low TSH level doesn’t indicate that Graves’ patients are still hyperthyroid. The TSH is generally suppressed due to the presence of stimulating TSH receptor antibodies.

Patients who are secreting TSH at all on a very low ATD dose or who are on alternative medicines are generally considered in remission. To tell, the meds are lowered further or given every second or third day. A repeat TSH level after 6-8 weeks should show a slight increase in TSH if remission has been achieved.

**Surgical Thyroid Removal (Thyroidectomy)**

Subtotal thyroidectomy is the oldest form of therapy used for GD. Surgery, both partial and total thyroidectomy, has the advantage of allowing direct tissue examination, and it offers prompt resolution of symptoms. After surgery, thyroid function returns to normal in between 90% and 98% of patients.

Thyroidectomy is a particularly good choice for patients with very large goiters since they seldom respond adequately to RAI. Surgery is also recommended for patients who plan to eventually become pregnant or patients who react severely to ATDs.

The surgical procedure most frequently used is a subtotal thyroidectomy in which a rim of each lobe is left, leaving a total of 4-6 grams. The thyroid is usually prepared to facilitate cutting by administering strong iodine solution for 7 to 10 days prior to surgery.

The mortality of thyroidectomy is close to zero. However, there are two rare complications, recurrent laryngeal nerve damage and hypoparathyroidism, which occur in 1% to 2% of cases. Both conditions can cause lifelong disability. Other transient complications include hypocalcemia, post-operative bleeding, wound infection, keloid formation, and scars. Finding a well experienced surgeon is of paramount importance.

Hypothyroidism is said to occur in 12% to 50% of patients in the first year after surgery, and late onset hypothyroidism develops in an additional 1% to 3% of patients each year, although this may be due to the natural progression of the disease. Recurrences may develop many years after surgery. 43% of recurrences occur within 5 years after surgery.

**Radioiodine Ablation (RAI)**

John Pacer, PhD, a physical chemist in Allentown, Pennsylvania, recently reminded me that radioisotopes are abundant in nature and work to maintain homeostasis by a process
of natural selection. Radioisotopes are present in many fruits, including bananas and
tomatoes, and in many types of wood.

Radioiodine, an isotope of iodine and a product of nuclear fission introduced in the mid-
1940’s, has become the most widely used treatment of adults with thyrotoxicosis in the
United States. It is also the cheapest and fastest form of therapy and has the most
potential to cause hypothyroidism. Radioiodine also releases autoantibodies into the
circulation and heightens the immune response, exacerbating symptoms and contributing
to a transient period of exaggerated symptoms. The release of stored hormone also causes
a temporary exacerbation of symptoms. These effects may cause thyroid storm. One
Graves’ patient, Sharon, developed thyroid storm 5 weeks after her radioiodine ablation.

The isotope I-131 is usually used for ablation. It is administered as an oral dose either as
a liquid where it is suspended in water or as a capsule. Thyroid cells can’t distinguish
between natural iodine and its radioisotopes so the thyroid follicular cells take up
radioiodine in the same way they absorb iodine.

Inside the body, radioiodine atoms release energy in the form of beta particles and
gamma rays, destroying or mutating whatever cells are at the end of their path length.
The immediate effect of radioiodine is cellular necrosis (death), which provokes an
inflammatory response. Tissue studies show bizarre nuclear changes "reminiscent of
carcinoma" which persist for many years.

Mutated cells are thought to be incapable of dividing although the increased rate of
thyroid cancer mortality in ablated patients in the Cooperative Thyrotoxicosis Therapy
Follow-up Study suggests otherwise. Since the cells of children divide at a greater rate
than those of adults, mutagenic effects are more pronounced in children. Although there
are no long-term studies on children treated with radioiodine, an increased incidence in
adenomas in children treated with external radiation has been demonstrated in more than
one study. Thus, radioiodine is contraindicated in children and women of childbearing
age.

**Half-Life**

Although radioiodine is said to have a half-life of 8 days, it is thought to take 8 to 10
cycles before all of it leaves the body. Dr. Pacer emphasized that side effects as well as
the time radioiodine actually leaves the body are dose related. If trillions of atoms are
initially delivered, imagine how long the reduction would take. Dr. Joseph Gong, a cell
biologist who studies the cumulative effects of radiation, says that radioiodine never fully
leaves the body. And the contributions from particles which do exit the body provide a
total body dose. A recent review of data from England’s Whickham Study shows a small
but significant increase in both thyroid and small bowel cancer mortality in ablated
patients.

There is no optimal dose for RAI. And protocols for determining an optimal dose are
controversial. Whatever method is used, calculations should take the thyroid volume and
radioiodine uptake test results into consideration. One recent European study recommended that doses not exceed 7,000 rad (70 Gy) if early hypothyroidism is to be avoided. Higher doses are associated with severe hypothyroidism. Thyroid function is reported to gradually decline within weeks to months after radioiodine treatment.

Radioiodine ablation has also been found to induce and/or exacerbate Graves’ ophthalmopathy (GO) and pretibial myxedema. A short course of prednisone used in conjunction with radioiodine helps in preventing the development of GO.

Although radioiodine is effective, its use is not without risk. And in many instances, it’s a form of overkill. I’m currently working on a project aimed at determining long-term chromosomal damage caused by RAI which is demonstrated by an increased number of red cells with transferrin receptors. I’ll share results on this board sometime in the next 6 months.

**Ionic Inhibitors**

In addition to the 3 major options, conventional medicine for GD occasionally employs ionic inhibitors, chemicals such as potassium perchlorate, which work like anti-thyroid drugs. At one time, these agents were used in extremely high doses which caused aplastic anemia and gastric ulcers. Since, they’ve been found to be effective at much lower doses. In the last decade, potassium perchlorate has been used with success in daily doses of 40 to 120 mg. Potassium perchlorate is also used in conjunction with ATD’s to treat iodine induced thyrotoxicosis and it’s effectively used in patients who are resistant to ATD therapy when ATDs are used as the sole agent.

**Beta Adrenergic Blocking Agents**

Beta adrenergic antagonist drugs are an integral part of the treatment protocol in Graves’ disease. Although they have no direct effect on thyroid function, they are valuable in ameliorating cardiac and nervous symptoms. While propranolol was the first drug of this class used to treat thyrotoxicosis, newer cardio selective agents such as esmolol, atenolol and metoprolol are also prescribed. Propranolol is primarily used since it has the advantage of inhibiting the conversion of thyroxine (T4) to the more potent triiodothyronine (T3).

Although propranolol is contraindicated in patients with bronchospasm and asthma, cardio selective drugs may be used in mild cases. Beta blockers are also contraindicated in congestive heart failure except when the heart failure is rate related or caused by atrial fibrillation. In diabetes, beta blockers are contraindicated because they may mask hypoglycemic symptoms. Beta blockers should not be used in patients with Brady arrhythmias, Raynaud’s phenomenon or to patients undergoing treatment with monoamine oxidase inhibitors.
While effective in improving negative nitrogen balance and decreasing oxygen consumption, heart rate and cardiac output, beta adrenergic blocking agents are seldom able to restore these measurements to normal except in the mildest cases. For this