

Thyroid Disease — Part 2

by H. David Bergman, Ph.D.

Dean, College of Pharmacy, Southwestern Oklahoma State University

Goals and Objectives

Goals:

To provide the pharmacist with information regarding the treatment of hypothyroidism and hyperthyroidism and their related problems.

Objectives:

After completing this article, the pharmacist should be able to:

1. Describe the treatments for hyperthyroidism.
2. Discuss the properties, uses, and side effects of the drugs used in the treatment of hyperthyroidism.
3. Describe the major complications of hyperthyroidism.
4. Describe the various forms of therapy for hypothyroidism and the differences between the major drugs.
5. Discuss the special problems associated with hypothyroidism.
6. Counsel patients regarding their therapy for thyroid disease.

E.L.F. Publications, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmaceutical education. This program has been approved for 1.5 contact hour (0.15 CEU).

Universal Program Number 406-000-07-002-H01.

The expiration date for this program is 2/05/10.



Both hyperthyroidism and hypothyroidism are treated by pharmacological intervention. Since they are chronic diseases, the pharmacist often evaluates therapy and provides counseling to patients regarding their treatment programs. Consequently, it is essential that the pharmacist understand the therapeutic management and complications associated with these disorders.

Treatment of Hyperthyroidism

Hyperthyroidism is treated with radioactive iodide (RAI), surgery, and antithyroid drugs. The selection of treatment is individualized and based on a variety of factors, such as the type of hyperthyroidism, the age of the patient, the severity, and the presence of complications.

Patients with toxic nodular disease frequently require surgery or RAI, while those with Graves' disease can often be treated medically until remission occurs. The decision in the uncomplicated patient should be made in consultation with the patient, and the risks and benefits of each method should be clearly outlined.

Surgery involves either total or subtotal thyroidectomy. It is used primarily in those patients who do not respond to other forms of therapy, those with a malignancy, in selected pregnant patients, and young children. The risk of this initial therapy is not great, provided the patient is in a euthyroid state. Complications occur more frequently if the patient requires additional surgery because of the problems associated with identifying structures.

Cardiac and/or respiratory disease as well as pregnancy in the third trimester (labor may be precipitated) are contraindications to surgery. Surgically induced problems include vocal cord paralysis, delayed wound healing, permanent hypoparathyroidism and hypothyroidism. Therefore, it is essential that this type of surgery, which has infrequent but severe complications, be performed by an experienced thyroid surgeon.

RAI is indicated in those patients with a history of prior surgery, with complicated disease, and in patients past adolescence who require this form of therapy. RAI should not be used during pregnancy. The most frequently used isotope is I^{131} which has a half-life of eight days and delivers high energy beta

radiation. The dose is based on gland size and is variable.

In patients with large stores of hormones or those with severe heart disease, pretreatment with antithyroid drugs or propranolol is recommended prior to RAI therapy. Iodides should not be used prior to RAI therapy because the uptake of RAI will be greatly impeded. A therapeutic response should be detected in two to three weeks with peak effects occurring in three to six months after the administration of RAI.

Although the slow onset is a disadvantage to RAI use, the administration of drugs can frequently control the symptoms. A second dose should not be administered for at least 6 months because ongoing radiation effects may still be occurring.

The primary complication of RAI therapy is hypothyroidism, which occurs in 10% of treated patients the initial year. The immediate side effects of RAI are minimal and include mild thyroidal pain and tenderness, transient thinning of hair and rare dysphagia.

Another method of using iodine to treat hyperthyroidism is the use of sodium ipodate, an iodinated contrast dye which contains more than 60 percent iodine. Like other iodinated contrast media (i.e., iopanoic acid), ipodate inhibits triiodothyronine production, but it is more potent. When ipodate is administered in doses of 500 milligrams to one gram orally each day or three grams every third day to thyrotoxic patients, improvement is seen. Ipodate is relatively nontoxic and is a useful therapeutic approach.

The most frequently used drugs to treat hyperthyroidism are the thioamides. Methimazole and propylthiouracil are the drugs used. They act by inhibiting the oxidation binding of iodide and its coupling to tyrosine residue. In addition, an immunosuppressive mechanism of action has been postulated. These drugs do not cure the underlying disease, but provide relief until remission hopefully occurs. Methimazole is ten times more potent than propylthiouracil, but the drugs are similar when used in equipotent doses. Both drugs are rapidly absorbed from the gastrointestinal tract and peak concentrations are achieved within 30 minutes.

The duration of action of propylthiouracil and methimazole is much longer than their respective half-lives of two and seven hours. The initial dose of propylthiouracil is 300 to 800 milligrams daily in four divided doses, while the daily dose of methimazole is 40 to 80 milligrams in three divided doses. Maintenance doses of propylthiouracil or its equivalent should be 50 to 300 milligrams daily, which, in some instances, may be administered as a single daily dose.

Before the dosage of antithyroid drugs should be tapered, a reduction of symptoms and lowering of serum thyroxine levels should be achieved, which usually requires one to two months therapy. Therapy is usually continued for 12 to 18 months. Prior to the initiation of therapy, baseline laboratory values and a white blood count with differential should be obtained. These should be used as parameters during therapy.

Adverse effects with propylthiouracil and methimazole include skin rashes, lupus-like syndromes, and agranulocytosis. Agranulocytosis is the most serious of these reactions, has a variable onset, and can be completely reversed after discontinuation of the drug. Patients should be aware of symptoms (e.g., fever, sore throat) and seek immediate attention. Propylthiouracil is transmitted into breast milk and crosses the placental barrier to a lesser degree than methimazole. These drugs are successful in about half the patients and enjoy a higher success rate in those patients with small goiters.

Potassium perchlorate is used in a one-gram daily dose. Potassium perchlorate is concentrated by the gland, interferes with iodide binding in the thyroid gland, and causes the release of the iodide from the gland. Perchlorate effects can be neutralized by iodine administration, since it is a competitive inhibitor of iodide. The use of perchlorate has been limited because it may cause nephrotic syndrome and irreversible aplastic anemia.

Lugol's solution and SSKI have been used to treat young patients with mild disease. Their long-term effectiveness is limited because the gland has the ability to "escape" between the second and third month of administration despite continued therapy. The dose of iodide used to treat hyperthyroidism is

six milligrams daily, but 40 to 80 milligrams of Lugol's solution is typically used. Iodides are often administered for two weeks prior to surgery to decrease the vascularity and increase the firmness of the gland, which enhances the surgical process.

Adverse effects associated with iodide therapy include skin rashes, rhinitis, drug fever, and conjunctivitis, which are considered to be hypersensitivity reactions to iodide.

Since many of the effects of hyperthyroidism are associated with adrenergic overactivity, sympatholytics have been employed to treat many of the major symptoms. Guanethidine and reserpine have been used successfully, but require several weeks to exert an effect and have frequent adverse effects which are primarily related to their hypotensive effects. Consequently, propranolol has replaced these drugs. Anxiety, tremor, diarrhea, palpitations and sweating are usually reduced when propranolol is administered in a 20 to 40 milligram dose four times per day. It is also valuable as an adjunct to RAI and thioamides as well as in pregnancy and prior to surgery. Patients with asthma, chronic pulmonary disease, congestive heart failure, or a recent history of myocardial infarction should be administered the drug very cautiously.

Lithium acts similarly to iodides in inhibiting thyroid hormone release. The dose employed is 800 to 1200 milligrams per day. Adverse effects of lithium include tremor, ataxia, vomiting, diarrhea, confusion and cardiac arrhythmias. Lithium should not be considered a first choice drug and is used when other drugs (i.e., iodides) are contraindicated.

Other Problems Associated with Hyperthyroidism

Although it is rare to find hyperthyroidism during pregnancy, treatment is a complex problem because the fetal thyroid begins functioning between the third and fourth months of pregnancy. RAI cannot be used because transplacental passage will destroy the fetal thyroid. Surgery can be performed during the second trimester, but may precipitate labor during the third trimester. Propylthiouracil in daily doses of less than 300 milligrams and maintenance doses of 100 to 150 milligrams can be used. Propranolol may also be used on a short-term basis, but chronic use may cause fetal problems.

Ophthalmologic complications are not well understood, but require various forms of therapy for a variety of problems. Protective glasses, hydrocortisone drops, and methylcellulose drops may be useful for external irritation and photophobia, while corneal scarring may be prevented by taping eyelids shut at night. In some patients, systemic corticosteroids (i.e., prednisone, in daily doses of 40 - 80 milligrams for one to two weeks) can be used to treat exophthalmos associated with decreased visual acuity, but the effects are unpredictable.

Children account for less than 5% of the cases of hyperthyroidism. The peak age of occurrence in children is 10 - 12 years. Symptoms are similar to those encountered in adults, but cardiovascular manifestations are not usually present. The usual therapy is antithyroid drugs or subtotal thyroidectomy. The risks and benefits associated with each method must be considered.

Thyroid storm is a medical emergency associated with acute onset of high fever, agitation, tachycardia, hyperglycemia, tachypnea, and psychosis progressing eventually to coma. This disorder acts as an overwhelming form of thyrotoxicosis and can be precipitated by stress, infection, trauma, post-RAI therapy, or the abrupt discontinuation of antithyroid medication. Treatment consists of appropriate support of vital functions, the use of antithyroid drugs to block synthesis and release of hormones, propranolol and/or sympathetic medications to overcome the major adrenergic symptoms, and removal of the precipitating factors.

Therapy for Hypothyroidism

Thyroid hormones are the major therapy for hypothyroidism. Their administration provides adequate replacement therapy for hypothyroidism as well as shrinkage of the goiter by suppression of thyroid stimulating hormone production. The initial dose of thyroxine or its equivalent depends on the duration and severity of the disease, the age of the patient, and the other problems or disorders of the patient (i.e., cardiac abnormalities) which may or may not be related to the hypothyroidism.

The typical patient who does not have chronic disease with complications is administered doses of 100 to 150 micrograms per day of thyroxine or its

equivalent. Elderly patients and/or those with chronic or severe disease with complications should initially be administered doses of less than 50 micrograms of thyroxine per day. These individuals are very sensitive to the metabolic effects of thyroid hormone, so that small doses must be used to avert major complications such as angina pectoris or tachycardia. If the initial doses are tolerated, then these can be increased every other week by 25 to 50 micrograms.

Congenital hypothyroidism is treated similarly. However, normal development and growth are a major concern. Therefore, it is important that adequate therapy be initiated in the early stages. Most children respond very well if the therapy begins before age three months. If treatment is not initiated until ages six months to one year, mental impairment often occurs.

Treatment beginning after five years of age or older does not appear to improve intelligence, but growth may be enhanced. In children with severe hypothyroidism, treatment may cause adverse effects, such as abnormal behavior in which the child may be uncontrollable. In these cases, it may be desirable to maintain the child in a very mild hypothyroid state. If the child has severe or chronic disease, very small doses of thyroid hormone should be used initially (i.e., 25 micrograms/day). As in the adult, this can be gradually increased based on response and toxicity (12.5 micrograms every other week). Typically, children between four and 12 years of age receive between 100 and 300 micrograms of thyroxine or its equivalent daily.

All of the preparations that are available commercially are effective for treating hypothyroidism. However, there are a variety of differences among the products which are the major determining factors in the selection process. Desiccated thyroid is obtained primarily from hog thyroids, but sheep and beef are also used. It is standardized with respect to iodine content, so that the ratio of hormones may vary, which can result in a variation in potency. This can cause an unpredictable response.

In addition, desiccated thyroid must be kept dry and appears to be stable for approximately five years. Improper storage or use of an old product may also

contribute to undesired response. Since the product does contain a protein component, some individuals have experienced allergic reactions. Despite these potential problems, desiccated thyroid has been both beneficial and economical therapy for many patients with hypothyroidism.

Unlike desiccated thyroid, thyroglobulin is purified hog extract which is biologically standardized to provide a 2.5 to one ratio of T_4 to T_3 . It has no therapeutic advantages over desiccated thyroid, but is somewhat more expensive.

L-thyroxine is a stable product with uniform potency which does not produce foreign protein reactions. It has a half-life of one week which allows for daily dosing and may also result in increased patient compliance. Although variable absorption has been reported, this has not been a major problem.

L-triiodothyronine or T_3 is a chemically pure agent with predictable potency and a half-life of 36 hours. It is not used very often to treat hypothyroidism because of the need for multiple daily dosing, cost, and the potential for increased cardiac adverse effects.

Liotrix is a combination of T_4 and T_3 in a ratio of 4:1 which is designed to parallel the natural secretion of hormones. Initially, this combination was recognized as an important advance in therapy. However, since it has been determined that significant amounts of T_4 are converted peripherally to T_3 , these more expensive products have become less popular. Although it does not appear to have any major advantage over other thyroid preparations, liotrix is pure, stable, and provides predictable potency.

Special Problems Related to Hypothyroidism

Myxedema coma is a condition which occurs at the end stage of chronic uncorrected hypothyroidism. Hypothermia, delayed deep tendon reflexes, and altered sensorium are major clinical features. In addition, hypoglycemia, hyponatremia, shock and psychosis can occur. Immediate therapy is needed in order to prevent death. The mortality rate for myxedema coma is greater than 50 percent. This

problem is precipitated by a variety of factors, including trauma, other uncontrolled diseases (cardiovascular disease), stress and/or infection.

Therapy with parenteral L-thyroxine and hydrocortisone is used. Supportive therapy for hypoglycemia, shock and hyponatremia is usually required. As soon as possible, the causative factors should be corrected.

Hypothyroidism during pregnancy has been associated with congenital defects, stillbirths, mental retardation, spontaneous abortion, and neonatal hypothyroidism. Thyroid hormone does not significantly cross the placental barrier to the fetus. Therefore, therapy can be conducted without harm to the fetus.

Thyroid Function and Other Effects

A variety of diseases and drugs are affected by thyroid function. The response to digitalis may be altered as thyroid status changes. Hypothyroid patients often have an increased sensitivity, while hyperthyroid patients often require increased doses of digitalis preparations. Patients with hyperthyroidism usually require smaller doses of warfarin to achieve the desired effect, while the half-life of clotting factors is prolonged in hypothyroidism which requires larger doses of warfarin to achieve adequate anticoagulation. Sympathomimetics may enhance thyrotoxic symptoms, particularly the cardiovascular effects, in hyperthyroidism. Concurrent administration of cholestyramine with thyroxine will result in a binding of thyroxine and a delay and possible reduction in absorption. Consequently, these drugs should not be administered on the same schedule.

Conclusion

Thyroid disorders affect a significant number of individuals in the United States. Pharmacologic intervention is the major mode of treatment for these chronic diseases. The pharmacist can provide an important role in patient education, counseling, and evaluation of therapy for hypothyroidism and hyperthyroidism.

Drugs Used To Treat Hypothyroidism

Generic Name	Example of Brand Name
Desiccated Thyroid	Armour Thyroid
Thyroglobulin	Proloid
L-thyroxine	Synthroid
L-triiodothyronine	Cytomel
Liotrix	Thyrolar Euthroid

Examples of Drugs Associated With Hyperthyroidism Therapy

Generic Name	Example Of Brand Name
Methimazole	Tapazole
Propylthiouracil	Propacil
Propranolol	Inderal
Prednisone	Sterapred
Reserpine	Serpasil
Guanethidine	Ismelin
Lithium Carbonate	Eskalith
Iodate	Oragrafin