



GRAVES' DISEASE & THYROID FOUNDATION

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Tapazole and Propylthiouracil in Graves' Disease by Timothy W. Lowrey, PharmD; Chalet A. DeCapito, PharmD; and William J. Millard, Ph.D.

Perhaps one of the first obstacles or uncertainties that a patient faces after being diagnosed with Graves' disease is deciding on the treatment choice for disrupting or halting the course of Graves' disease. Since Graves' disease is an autoimmune disorder that affects the functioning of the thyroid gland, a reasonable choice of therapy would be to try to correct the alteration in the immune system that initiated the disease.

However, this therapeutic approach has yet to be perfected. Therefore, the alternative course of treatment of Graves' disease is to control the excessive production and release of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), from the thyroid gland.

Currently, there are three acceptable treatment regimens which can be utilized to reduce thyroid activity in a patient with Graves' disease. These treatment choices include: 1)

medical or drug therapy to control excessive hormone production by the thyroid gland; 2) radioactive iodine therapy to selectively destroy the thyroid gland and; 3) surgical removal of all or part of the thyroid gland. It is important for the physician to inform the patient about all three therapeutic options, their benefits and drawbacks, and the optimal approach for treatment of each individual with Graves' disease.

With respect to medical or drug therapy for a patient recently diagnosed with Graves' disease the use of selective drugs (antithyroid drugs) to reduce thyroid activity can be employed. Therefore, it is important that each individual with Graves' disease be informed of all aspects of the commonly used antithyroid drugs. In North America the two principal antithyroid drugs are methimazole (Tapazole®) and propylthiouracil (PTU). These antithyroid agents belong to a class of drugs called the

thionamides or thioamides. Outlined below is a summary of the action and dosing of the thionamides along with their associated side effects and possible drug interactions.

Mechanism of Action of Thionamides

Neither Tapazole® nor PTU destroy the thyroid gland, nor do these agents prevent the release of previously formed or stored thyroid hormones from the thyroid gland. Both Tapazole® and PTU principally act to decrease formation of newly synthesized thyroid hormones (T4 and T3) in the thyroid gland. Both agents block new thyroid hormone formation by interfering with the incorporation of iodine, an element essential for the biological activity of the thyroid hormones, into the thyroid hormone molecule. PTU but not Tapazole® has the additional capacity of blocking conversion of the major thyroid hormone T4 to

its more biologically active form T3.

Because the thyroid has the capacity to synthesize and store very large quantities of T4 and T3, a reduction in thyroid activity generally is not seen immediately after initiation of antithyroid drug therapy. Instead, a period of 3-6 weeks of drug therapy may be required before a demonstrable reduction in thyroid activity is found. It is imperative that once antithyroid drug treatment is initiated, it is maintained on a daily basis until a doctor determines that drug therapy should be changed or discontinued. Failure to comply will only result in a delay in the improvement of the hyperthyroid condition and ultimate maintenance of normal thyroid function.

Indications and Uses of Thionamides

Both Tapazole® and PTU are indicated for the treatment of all forms of hyperthyroidism including Graves' disease. In a patient with advanced stages of hyperthyroidism that will require thyroid surgery or radioactive iodine therapy, these agents are utilized to lower thyroid activity prior to surgery or radioiodine treatment. PTU, because of its ability to block conversion of T4 to T3, is

also indicated as the preferred thionamide in the treatment of thyroid storm.

Formulations and Dosing of Thionamides

[Editor's update: new guidance was released in 2011 regarding reduced initial and maintenance dosing of Tapazole® and PTU. The guidance also states that PTU is associated with an unacceptable risk of liver failure in children and that methimazole (brand name Tapazole®) is preferred over PTU for all patients, except in select circumstances. For more information, please see "*Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists*" by Bahn, et. al at thyroidguidelines.net.]

Both Tapazole® and PTU are taken by mouth in tablet form and in varying concentrations. Because Tapazole® is more potent than PTU, the usual daily dosage of Tapazole® is lower than that of PTU. The dose of either antithyroid agent is adjusted to each individual patient on the basis of both thyroid function tests and observed therapeutic responses. Therefore, to

obtain optimal results of antithyroid drug therapy compliance is essential. The proper scheduling and dosing of antithyroid drugs should be determined by a physician.

The range of thionamide doses utilized for initial drug therapy in patients with Graves' disease is 15-60 mg/day for Tapazole® taken once a day and 300-900 mg/day for PTU taken in divided doses until a normal thyroid state is reached. Once normal thyroid functioning is achieved (which may vary from 6 weeks or longer depending upon the severity of the Graves' disease), antithyroid drug doses are reduced (5-30 mg/day for Tapazole® and 50-300 mg/day for PTU) and generally administered once a day.

Because food may interfere with absorption of drugs from the gastrointestinal tract, it is advisable to take both Tapazole® and PTU every day at the same time in relation to meals.

Precautions Pregnancy and Reproduction

Both Tapazole® and PTU cross the placenta and cause hypothyroidism in the fetus. Therefore, if pregnancy is contemplated or one is already pregnant and currently taking

thionamides, a doctor should be contacted immediately. PTU is the drug of choice during pregnancy because Tapazole® more readily crosses the placenta and has been associated with scalp lesions in the fetus.

Lactation and Breast-feeding

Thionamides are absorbed and excreted into the breast milk, thus putting the infant at risk of developing hypothyroidism. Therefore, if one is currently breast feeding and taking either Tapazole® or PTU a doctor should be notified immediately. PTU is the preferred drug in nursing mothers because the concentrations of PTU are lower in breast milk.

Leukopenia

Infrequently thionamides have been shown to cause leukopenia (low white blood cell counts), thus increasing the risk of bacterial infection. Therefore, any patient who already has leukopenia either related to disease or induced by specific drugs (i.e. glucocorticoids) should notify their doctor prior to initiating thionamide therapy.

Adverse Effects of Thionamides

The frequency and severity of adverse effects from the thionamides are related to the drug dose. Adverse effects are usually experienced within the first 4 to 8 weeks of drug therapy. The most common adverse effect of thionamides relate to an allergic reaction to the medication and occurs in approximately 3-5% of patients. Other adverse effects such as reduced white blood cell counts (leukopenia), altered blood clotting, arthritis or hepatitis, occur less frequently or are rarely found.

Immediate medical attention should be sought if any of the following are experienced: skin rash or itching, pinpoint red spots on the skin, fever, chills, cough or hoarseness, throat or ear infection, mouth sores, unusual bleeding or bruising, blood in urine or stool, pain or swelling or redness in joints, side or lower back pain, pain or difficulty in urination, swollen lymph nodes, or yellow tint to eyes or skin.

One should seek medical attention only if any of the following conditions are persistent or bothersome: dizziness, nausea, vomiting, loss of taste, numbness or tingling in the face, hands or feet, or stomach pain.

Continued use of either Tapazole ® or PTU can result

in a significant reduction of thyroid gland activity or hypothyroidism. Therefore, each patient should be aware of the signs or symptoms of hypothyroidism. These signs include: sensitivity to cold, dry or puffy skin, constipation, sleepiness, listlessness, weakness, alteration in menstrual periods, hair loss, headache, or unusual weight gain. A physician should be contacted immediately if any of these signs of hypothyroidism are experienced. If any other side effects not listed above occur while you are taking Tapazole® or PTU one should notify and inform a doctor or pharmacist immediately.

Drug Interactions of Thionamides

A number of drug interactions can occur during the course of antithyroid drug therapy. Hyper-thyroid patients, because of increased metabolic activity, have increased metabolism and clearance of most drugs. Therefore, hyperthyroid patients who are also taking other medications generally require somewhat higher doses of the drugs. During antithyroid therapy overall metabolic activity of the patient decreases, thus, requiring that the dose of other drugs and, perhaps, the

thionamide itself may have to be adjusted.

Notable drugs that may interact with either Tapazole® or PTU include: bone marrow depressants (e.g. glucocorticoids), anticoagulants (e.g. Coumadin® or heparin), iodinated glycerol, lithium (e.g. Lithane®), or potassium iodide (e.g Pima®).

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