

REVIEW ARTICLE

DRUG THERAPY

Antithyroid Drugs

David S. Cooper, M.D.

ANTITHYROID DRUGS, WHICH HAVE BEEN IN USE FOR MORE THAN HALF a century, remain cornerstones in the management of hyperthyroidism, especially for patients with Graves' disease. Surveys of thyroidologists from the early 1990s indicate that most practitioners consider antithyroid drugs the treatment of choice for most young people with Graves' disease, both in the United States and in the rest of the world.^{1,2} A substantial amount of new information, much of it evidence-based,³ has become available since the topic was last summarized in the *Journal* in 1984.⁴ The present review considers recent pharmacologic and clinical data related to the use of these compounds.

From the Division of Endocrinology, Sinai Hospital of Baltimore, the Johns Hopkins University School of Medicine, Baltimore. Address reprint requests to Dr. Cooper at the Division of Endocrinology, Sinai Hospital of Baltimore, 2401 W. Belvedere Ave., Baltimore, MD 21215, or at dcooper@lifebridgehealth.org.

N Engl J Med 2005;352:905-17.

Copyright © 2005 Massachusetts Medical Society.

PHARMACOLOGY

MECHANISM OF ACTION

Antithyroid drugs are relatively simple molecules known as thionamides, which contain a sulfhydryl group and a thiourea moiety within a heterocyclic structure (Fig. 1). Propylthiouracil (6-propyl-2-thiouracil) and methimazole (1-methyl-2-mercaptoimidazole, Tapazole) are the antithyroid drugs used in the United States. Methimazole is used in most of Europe and Asia, and carbimazole, a methimazole analogue, is used in the United Kingdom and parts of the former British Commonwealth. These agents are actively concentrated by the thyroid gland against a concentration gradient.⁵ Their primary effect is to inhibit thyroid hormone synthesis by interfering with thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin, an important step in the synthesis of thyroxine and triiodothyronine (Fig. 2).

These medications possess other noteworthy effects (Fig. 3). First, propylthiouracil, but not methimazole or carbimazole, can block the conversion of thyroxine to triiodothyronine within the thyroid and in peripheral tissues, but this effect is not clinically important in most instances. Second, antithyroid drugs may have clinically important immunosuppressive effects. In patients taking antithyroid drugs, serum concentrations of antithyrotropin-receptor antibodies decrease with time,⁸ as do other immunologically important molecules, including intracellular adhesion molecule 1⁹ and soluble interleukin-2 and interleukin-6 receptors.^{10,11} In addition, there is evidence that antithyroid drugs may induce apoptosis of intrathyroidal lymphocytes,¹² as well as decrease HLA class II expression.¹³ Also, most studies show an increased number of circulating suppressor T cells and a decreased number of helper T cells,¹⁴ natural killer cells,^{15,16} and activated intrathyroidal T cells¹⁴ during antithyroid-drug therapy.

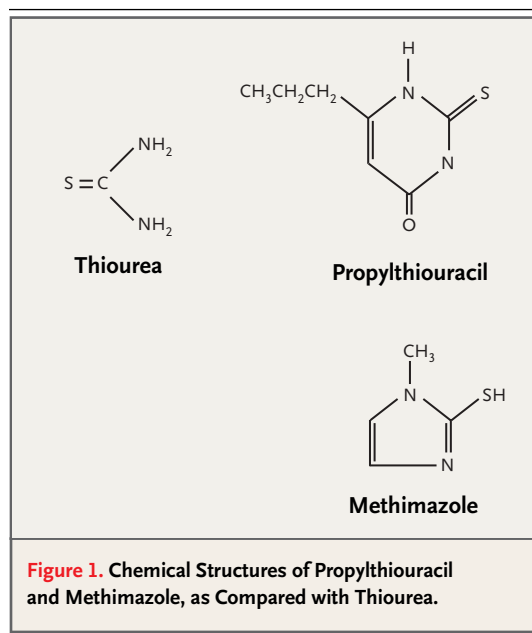
Despite these multiple lines of evidence, it has been argued that any change in the immune system must be viewed in the context of a drug-induced simultaneous improvement in thyroid function that could itself have a beneficial effect on the autoimmune process in patients with Graves' disease.¹⁷ However, analyses of animal data^{18,19} and human studies²⁰ have also suggested that changes in the immune system may not be predicated solely on changes in thyroid function.

CLINICAL PHARMACOLOGY

Both propylthiouracil and methimazole are rapidly absorbed from the gastrointestinal tract, peaking in serum within one to two hours after drug ingestion.^{21,22} Serum levels have little to do with antithyroid effects, which typically last from 12 to 24 hours for propylthiouracil²³ and possibly even longer for methimazole.^{24,25} The long duration of action of methimazole allows once-daily dosing, whereas propylthiouracil is usually given two or three times per day.^{26,27} The two drugs differ in their binding to serum proteins. Methimazole is essentially free in serum, whereas 80 to 90 percent of propylthiouracil is bound to albumin. The doses of these drugs do not need to be altered in children,²⁸ the elderly,²⁹ or persons with renal failure.^{30,31} No dose adjustment is needed in patients with liver disease, although the clearance of methimazole²² (but not propylthiouracil³²) may be decreased.

CLINICAL USE OF DRUGS

In general, antithyroid drugs are used in two ways: as the primary treatment for hyperthyroidism or as preparative therapy before radiotherapy or surgery (Fig. 4). Antithyroid drugs are most often used as the primary treatment for persons with Graves' disease, in whom "remission," which is usually defined as remaining biochemically euthyroid for one year after cessation of drug treatment, is possible.

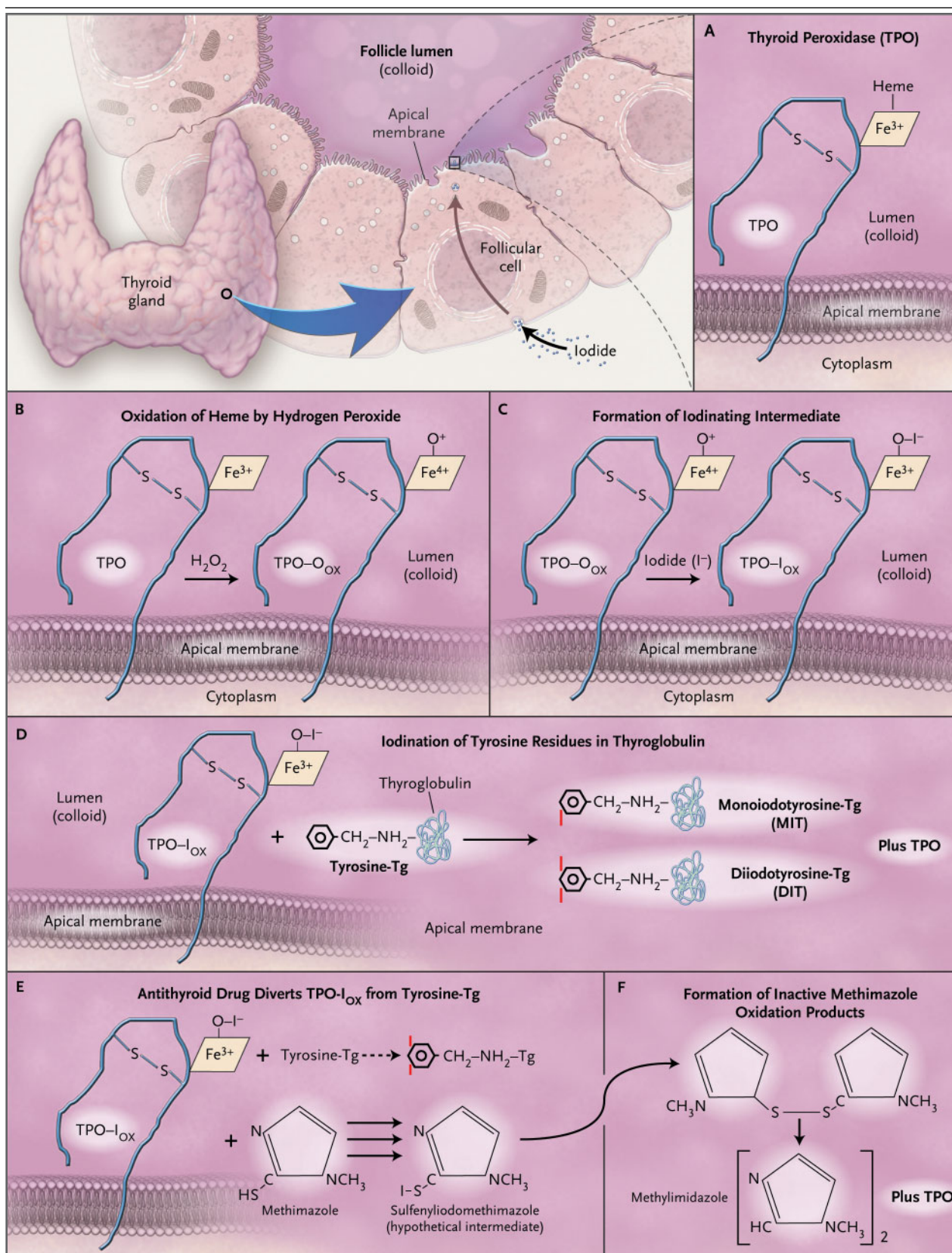


In contrast, antithyroid drugs are not generally considered to be primary therapy for patients with toxic multinodular goiters and solitary autonomous nodules, because spontaneous remissions rarely occur. Antithyroid drugs are also the preferred primary treatment in pregnant patients and in most children and adolescents. The decision to use antithyroid drugs as primary treatment must be weighed against the risks and benefits of the more definitive therapy that radioiodine and surgery provide. For example, antithyroid drugs might be preferable in patients with severe Graves' eye disease, in whom radioiodine therapy has been associated with worsening ophthalmopathy.³³

The preference of the patient is paramount in the decision process. A prospective randomized trial comparing antithyroid drugs, radioiodine, and surgery showed that patient satisfaction was more than 90 percent for all three,³⁴ but medical costs were lowest for antithyroid drug treatment.³⁵ Antithyroid drugs are also used to normalize thyroid function before the administration of radioiodine, because their administration may attenuate potential exacerbations following ablative radioiodine

Figure 2 (facing page). Synthesis of Thyroxine and Triiodothyronine.

In Panel A, thyroid peroxidase (TPO), a heme-containing glycoprotein, is anchored within the thyroid follicular-cell membrane at the luminal side of the thyroid follicle. In Panel B, the first step in thyroid hormone synthesis involves generation of an oxidized enzyme promoted by endogenously produced hydrogen peroxide. In Panel C, the oxidized enzyme reacts with trapped iodide to form an "iodinating intermediate" (TPO-I_{ox}), the nature of which is not entirely understood. Some investigators favor the formation of a heme-linked iodinium ion (TPO-I⁺), whereas others suggest the formation of hypoiodite (TPO-O-I⁻). In Panel D, in the absence of an antithyroid drug, the iodinating intermediate reacts with specific tyrosine residues in thyroglobulin (Tg) to form monoiodotyrosine and diiodotyrosine. Subsequent intramolecular coupling of MIT and DIT forms triiodothyronine, and the coupling of two DIT molecules forms thyroxine. In the presence of an antithyroid drug (e.g., methimazole, shown in Panel E), the drug serves as an alternative substrate for the iodinating intermediate, competing with thyroglobulin-linked tyrosine residues and diverting oxidized iodide away from hormone synthesis. The drug intermediate with a sulfur-linked iodide is a theoretical reaction product.⁶ In Panel F, the oxidized drug forms an unstable drug disulfide⁷ that spontaneously degrades to an inactive desulfurated molecule, shown as methylimidazole. Antithyroid drugs also impair the coupling reaction *in vitro*, but it is uncertain whether this occurs *in vivo*.



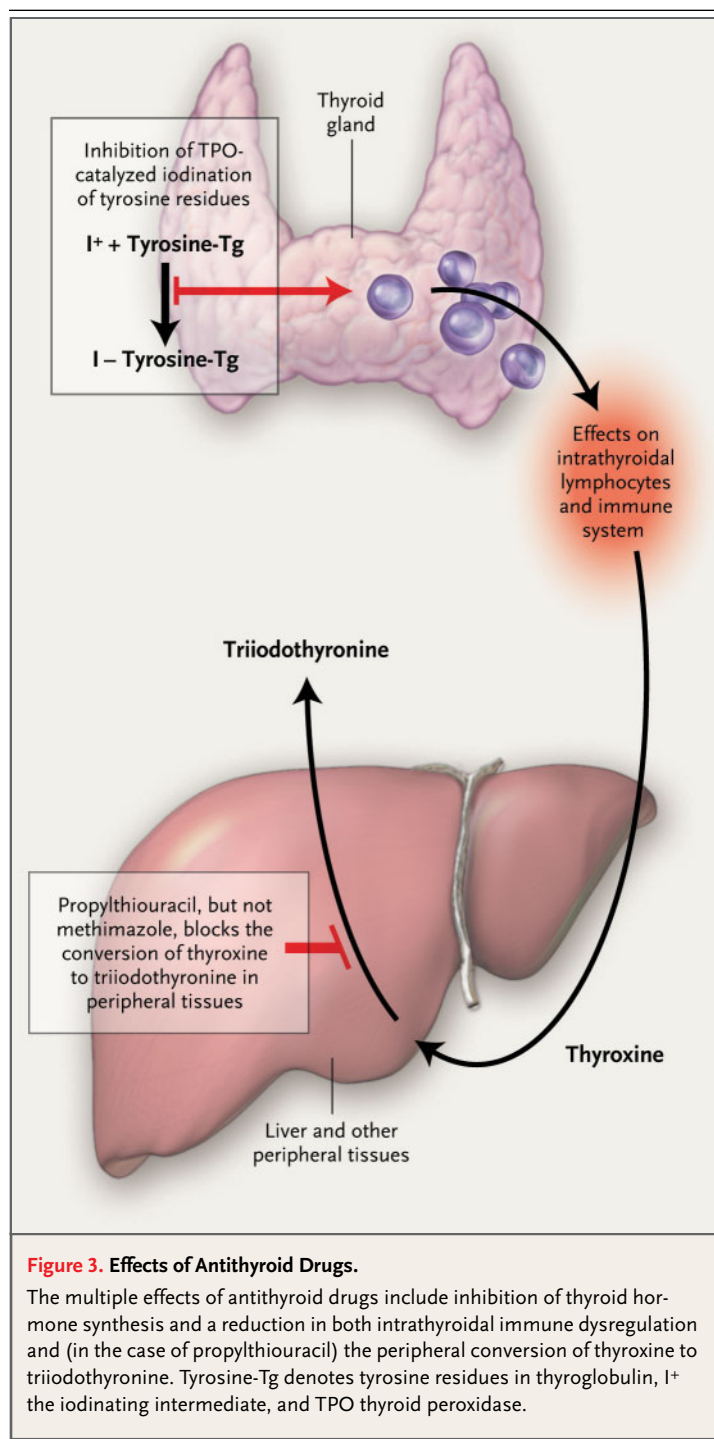


Figure 3. Effects of Antithyroid Drugs.

The multiple effects of antithyroid drugs include inhibition of thyroid hormone synthesis and a reduction in both intrathyroidal immune dysregulation and (in the case of propylthiouracil) the peripheral conversion of thyroxine to triiodothyronine. Tyrosine-Tg denotes tyrosine residues in thyroglobulin, I^+ the iodinating intermediate, and TPO thyroid peroxidase.

two groups that may be more vulnerable to worsening thyrotoxicosis.

CHOICE OF DRUGS

The choice between the drugs available in the United States, methimazole and propylthiouracil, has traditionally been a matter of personal preference. Nevertheless, methimazole, with its once-daily schedule, has decided advantages over propylthiouracil, including better adherence²⁷ and more rapid improvement in serum concentrations of thyroxine and triiodothyronine.^{27,39-41} The cost of low-dose generic methimazole is similar to that of propylthiouracil. In a recent search of Internet pharmacies,⁴² a one-year supply of propylthiouracil (300 mg daily) was approximately \$408, as compared with a one-year supply of methimazole (15 mg daily, \$360; or 30 mg daily, \$720). Finally, differences in the side-effect profiles of the two drugs favor methimazole. As discussed below, propylthiouracil is preferred during pregnancy.

PRACTICAL CONSIDERATIONS

The usual starting dose of methimazole is 15 to 30 mg per day as a single daily dose, and the usual starting dose of propylthiouracil is 300 mg daily in three divided doses. However, the disease of many patients can be controlled with smaller doses of methimazole, suggesting that the accepted potency ratio of 10:1 for methimazole as compared with propylthiouracil is an underestimate. In one randomized trial, 85 percent of patients had normal levels of thyroxine and triiodothyronine after six weeks of treatment with 10 mg of methimazole daily, as compared with 92 percent of patients receiving 40 mg daily.⁴³ Indeed, iatrogenic hypothyroidism may develop in patients with relatively mild hyperthyroidism if methimazole dosing is overly aggressive.⁴⁴ On the other hand, inadequate dosing will lead to continuing unmitigated hyperthyroidism.

Once a patient has been started on an antithyroid drug, follow-up testing of thyroid function every four to six weeks is recommended, at least until thyroid function is stable or the patient becomes euthyroid. After 4 to 12 weeks, most patients have improved considerably or have achieved normal thyroid function, after which the drug dose can often be decreased while maintaining normal thyroid function. The disease of many patients can be ultimately controlled with a relatively low dose—for example, 5 to 10 mg of methimazole or 100 to

therapy,³⁶ which are likely caused by a rise in stimulating antithyrotropin-receptor antibodies following radioiodine therapy.³⁷ Pretreatment with antithyroid drugs is therefore recommended for patients with underlying cardiac disease or for the elderly,³⁸

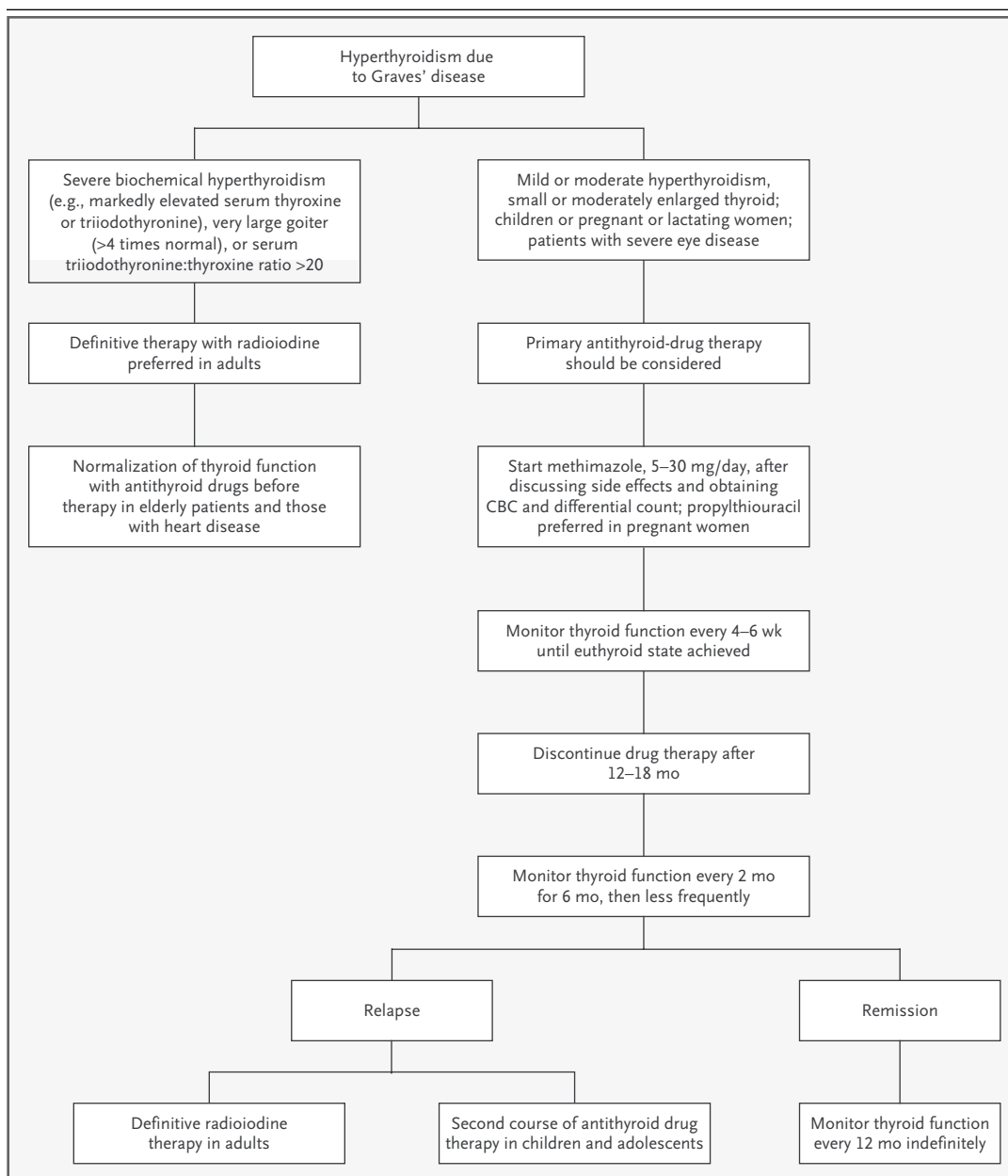


Figure 4. Algorithm for the Use of Antithyroid Drugs among Patients with Graves' Disease.

Antithyroid drugs are an option for initial therapy in adults with mild-to-moderate hyperthyroidism or active ophthalmopathy and are the therapy of choice for children, adolescents, and pregnant or lactating women. Radioiodine may be preferable as initial therapy for adults in the United States¹ but not for those in the rest of the world.² Subtotal or near-total thyroidectomy is also an option for some patients after treatment with antithyroid drugs. In adults who have a relapse, definitive radioiodine therapy is the preferred strategy. Some patients prefer a second course of antithyroid-drug therapy, and this strategy is preferable for children and adolescents. CBC denotes complete blood count.

200 mg of propylthiouracil daily. Indeed, hypothyroidism or goiter can develop if the dose is not decreased appropriately. After the first three to six months, follow-up intervals can be increased to

every two to three months and then every four to six months. Serum thyrotropin levels remain suppressed for weeks or even months, despite a normalization of thyroid hormone levels, so a test of

thyrotropin levels is a poor early measure. Furthermore, patients sometimes continue to have elevated serum triiodothyronine levels despite normal or even low thyroxine or free thyroxine levels, indicating the need to increase, not decrease, the antithyroid drug dose.⁴⁵

REMISSION

Clinicians have long sought clinical and laboratory predictors to improve the selection of patients so that only those patients most likely to have a remission would be subjected to the potential risks and inconvenience of antithyroid-drug therapy. In addition, there have been attempts to develop more effective strategies for the use of antithyroid drugs to enhance the chances of remission, including altering the dose and treatment duration and combining antithyroid drugs with thyroxine therapy.

Many retrospective studies clearly show that patients with more severe degrees of hyperthyroidism, large goiters, or a high triiodothyronine-to-thyroxine ratio in the serum (when unitless, more than 20) are less likely to enter remission after a course of drug treatment than are those with milder disease and smaller goiters.⁴⁶⁻⁴⁸ In addition, patients with higher baseline levels of antithyrotropin-receptor antibodies probably have a lower likelihood of remission.^{47,49}

Other clinical features that have been examined as possible predictors, but with inconsistent findings, include the patient's age, sex, and history of cigarette smoking; the presence or absence of ophthalmopathy; and the duration of symptoms before diagnosis. A recent prospective study showed that depression, hypochondriasis, paranoia, mental fatigue, and "problems of daily life" were risk factors for relapse after an average of three years of antithyroid-drug therapy.⁵⁰ Unfortunately, none of these parameters have sufficient sensitivity or specificity to be clinically useful in predicting the ideal candidates for primary drug therapy. Indeed, a prospective study of more than 300 patients with Graves' disease was unable to identify any clinical or biochemical marker that predicted remission or relapse after 12 months of antithyroid-drug therapy.⁴⁸ Measurement of antithyrotropin-receptor antibodies at the end of a course of treatment may have predictive value, in that antibody-positive patients almost always have a relapse.^{51,52} However, even those patients whose antibody titers have normalized have a fairly high rate of relapse (30 to 50 percent).^{53,54}

If antithyroid drugs have immunosuppressive effects, a higher dose or longer treatment duration might enhance the chances of remission. At least six prospective randomized trials have examined possible benefits of high-dose drug therapy as compared with lower doses. With the exception of one trial,⁵⁵ all have been negative.^{48,56-59} With regard to treatment duration, one prospective trial showed a significant improvement in the rate of relapse after 2 years of follow-up in patients treated for 18 months, as compared with those treated for 6 months (42 percent vs. 62 percent).⁶⁰ However, data from other prospective trials with up to four years of follow-up do not indicate that treatment for longer than one year has any effect on relapse rates.^{61,62}

Given these results, treatment with antithyroid drugs for 12 to 18 months is the usual practice, as recommended in a recent systematic, evidence-based review.⁶³ Some patients opt for long-term antithyroid drug treatment (i.e., years or even decades), and there is no theoretical reason why a patient whose disease is well controlled with a small dose of antithyroid drug could not continue antithyroid-drug therapy indefinitely.⁶⁴ Finally, a Japanese study showed that a combination of an antithyroid drug plus thyroxine for one year, followed by thyroxine alone for three years, decreased the relapse rate significantly.⁶⁵ However, subsequent attempts to replicate this study have failed.⁶⁶⁻⁶⁸

DISCONTINUATION OF DRUG TREATMENT

With the exception of children and adolescents, who are often treated with antithyroid drugs for many years, antithyroid drugs are usually stopped or tapered after 12 to 18 months of therapy. The likelihood of relapse is increased in patients with normal serum levels of free thyroxine and triiodothyronine but suppressed serum thyrotropin levels.⁶⁹ Relapse usually occurs within the first three to six months after medication is stopped.⁴⁷ Thereafter, the rate of recurrence decreases and plateaus after one to two years, for an overall recurrence rate of approximately 50 to 60 percent.^{48,70,71} About 75 percent of women in remission who become pregnant will have a postpartum relapse of Graves' disease or the development of postpartum thyroiditis.⁷² Lifelong follow-up is required for patients in remission, since spontaneous hypothyroidism may develop decades later in some of them.⁷³

It is important that the possibility of relapse be discussed so that a treatment strategy will be in

place in the event of recurrence. If radioiodine therapy is selected after a relapse, the outcome may be influenced by the prior use of antithyroid drugs. When used to normalize thyroid function before radioiodine therapy, propylthiouracil, but not methimazole, increases the failure rate of the radioactive iodine.^{36,74-76} This “radioprotective” effect of propylthiouracil may be related to its ability to neutralize iodinated free radicals produced by radiation exposure, a property evidently not shared by methimazole.⁷⁵ The radioprotective effect can be overcome by increasing the radioiodine dose.

SIDE EFFECTS

Antithyroid drugs are associated with a variety of minor side effects, as well as potentially life-threatening or even lethal complications.⁷⁷⁻⁷⁹ Side effects of methimazole are dose-related, whereas those of propylthiouracil are less clearly related to dose.⁷⁷ This may favor use of low-dose methimazole rather than propylthiouracil in the average patient with hyperthyroidism. In a review of the literature, it was found that “minor” side effects that included cutaneous reactions (usually urticaria or macular rashes), arthralgia, and gastrointestinal upset occurred in approximately 5 percent of patients, with equal frequency for both drugs.⁷⁷ Minor cutaneous reactions may resolve when an antihistamine is added while drug therapy is continued. As an alternative, a patient might be switched from one antithyroid drug to the other. However, cross-reactivity between the two agents may be as high as 50 percent. Abandoning antithyroid drugs is a third option, to be followed by definitive radioiodine therapy. The development of arthralgias, while classified as a “minor” reaction, should prompt drug discontinuation, since this symptom may be a harbinger of a severe transient migratory polyarthritis known as “the antithyroid arthritis syndrome.”⁸⁰

Agranulocytosis is the most feared side effect of antithyroid-drug therapy. In the largest series, agranulocytosis (an absolute granulocyte count of less than 500 per cubic millimeter) occurred in 0.37 percent of patients receiving propylthiouracil and in 0.35 percent receiving methimazole.⁸¹ Agranulocytosis must be distinguished from the transient, mild granulocytopenia (a granulocyte count of less than 1500 per cubic millimeter) that occasionally occurs in patients with Graves’ disease, in some patients of African descent, and occasionally in patients treated with antithyroid drugs. A baseline dif-

ferential white-cell count should be obtained before initiation of therapy.

Most cases of agranulocytosis occur within the first 90 days of treatment, but this complication can occur even a year or more after starting therapy. Some, but not all, studies have suggested that the risk of agranulocytosis is greater in older patients and that they have a higher rate of death.⁸² It is important to note that agranulocytosis can develop after a prior uneventful course of drug therapy, a finding that is important since renewed exposure to the drug frequently occurs when patients have a relapse and undergo a second course of antithyroid therapy.

Agranulocytosis is thought to be autoimmune-mediated, and antigranulocyte antibodies are shown by immunofluorescence⁸³ and cytotoxicity^{84,85} assays. Antineutrophil cytoplasmic antibodies may play a role, since antigen targets (e.g., proteinase 3) may be expressed on the neutrophil surface.⁸⁶ Routine monitoring of granulocyte counts in patients receiving antithyroid drugs has not been considered cost-effective, a viewpoint that has been challenged by a report indicating that asymptomatic patients may be detected through monitoring and “rescued” by stopping the antithyroid drug and administering granulocyte colony-stimulating factor (G-CSF).⁸⁷ Nevertheless, most authorities still do not recommend routine monitoring of the blood count.^{88,89} However, all patients should be instructed to discontinue the antithyroid drug and contact a physician immediately if fever or sore throat develops. A white-cell count and differential count should be obtained immediately and the drug discontinued if the granulocyte count is less than 1000 per cubic millimeter, with close monitoring of the granulocyte count if it is more than 1000 per cubic millimeter but less than 1500 per cubic millimeter.

Fever and sore throat are the most common presenting symptoms of agranulocytosis,⁹⁰ but sepsis should be suspected if there is very rapid onset of fever, chills, and prostration. In such cases, antithyroid drugs should be immediately discontinued and the patient should be hospitalized. According to one report, *Pseudomonas aeruginosa* was the species most commonly isolated from the blood in agranulocytosis-associated sepsis.⁹⁰ Therapy for agranulocytosis consists of the intravenous administration of broad-spectrum antibiotics (including coverage for possible pseudomonas infection) among patients who are febrile or who have obvious infections.

The administration of G-CSF may shorten the time to recovery and length of hospitalization in patients with agranulocytosis due to antithyroid drugs.⁹¹ A bone marrow aspirate may be useful prognostically, since severe depression of myeloid precursors suggests a prolonged recovery time and a failure to respond to G-CSF.^{92,93} Although a prospective randomized, controlled trial showed no significant difference in recovery time between no treatment and G-CSF therapy,⁹⁴ most authorities recommend using G-CSF for agranulocytosis due to antithyroid drugs.⁹⁰⁻⁹³ Cross-reactivity between propylthiouracil and methimazole for agranulocytosis has been well documented, so the use of the alternative antithyroid drug is contraindicated.

Hepatotoxicity is another major side effect of antithyroid drugs. Estimates regarding the frequency of this condition are imprecise, but it probably ranges from 0.1 percent to 0.2 percent.⁷⁷ The recognition of propylthiouracil-related hepatotoxicity may be difficult, since in up to 30 percent of patients with normal baseline aminotransferase levels who are treated with propylthiouracil, transient acute increases in those levels develop, ranging from 1.1 to 6 times the upper limit of normal — levels that resolve while therapy is continued.⁹⁵ Also, asymptomatic elevations in serum aminotransferase levels occur frequently in untreated patients with hyperthyroidism and are not predictive of further increases after the institution of propylthiouracil therapy.⁹⁶

The average duration of propylthiouracil therapy before the onset of hepatotoxicity is approximately three months.⁹⁷ Propylthiouracil-related hepatotoxicity takes the form of an allergic hepatitis accompanied by laboratory evidence of hepatocellular injury — often markedly elevated aminotransferase levels and submassive or massive hepatic necrosis on biopsy. Therapy consists of immediate cessation of propylthiouracil along with expectant management of the potential complications of hepatic failure. Although the literature suggests a case fatality rate of 25 to 50 percent,⁹⁸ it is likely that milder cases that resolve uneventfully are never reported. Liver transplantation may be required,⁹⁹ and referral to a specialized center is reasonable. Routine monitoring of liver-function tests in patients being treated with propylthiouracil is generally not recommended, given the frequent benign liver-function abnormalities noted earlier.

The rare hepatic abnormalities associated with methimazole and carbimazole are typical of a chole-

static process.¹⁰⁰ Biopsy specimens show preserved hepatocellular architecture, along with intracanalicular cholestasis and mild periportal inflammation. Complete, but slow, recovery is the rule after drug discontinuation. Since the mechanisms of hepatotoxicity for the two antithyroid drugs used in the United States differ, the alternative agent could be used cautiously to treat the underlying hyperthyroidism in a patient with complicated thyrotoxicosis and drug-induced hepatic side effects.^{100,101}

Vasculitis is the third major toxic reaction seen with antithyroid-drug treatment, more commonly found in connection with propylthiouracil than with methimazole. Serologic evidence consistent with lupus erythematosus develops in some patients, fulfilling the criteria for drug-induced lupus.¹⁰² Antineutrophil cytoplasmic antibody-positive vasculitis has also been reported, especially in Asian patients treated with propylthiouracil.¹⁰³ Most patients have perinuclear antineutrophil cytoplasmic antibodies, with a majority of them having antimyeloperoxidase antineutrophil cytoplasmic antibodies.¹⁰⁴ It has been hypothesized that antithyroid drugs, especially propylthiouracil, can react with myeloperoxidase to form reactive intermediates that promote autoimmune inflammation.^{105,106}

The clinical features of drug-induced antineutrophil cytoplasmic antibody-positive vasculitis include acute renal dysfunction, arthritis, skin ulcerations, vasculitic rash, and upper and lower respiratory symptoms, including sinusitis and hemoptysis. Although this syndrome generally resolves after drug cessation, high-dose glucocorticoid therapy or cyclophosphamide may be needed in severe cases, and some patients have required short-term hemodialysis. Some patients with Graves' disease may have positive tests for antineutrophil cytoplasmic antibody before therapy.^{107,108} In a large cross-sectional study from the United Kingdom,¹⁰⁹ antineutrophil cytoplasmic antibody positivity was detected in 5 percent of 649 normal euthyroid control subjects, 4 percent of untreated patients with Graves' disease, 33 percent of patients receiving propylthiouracil, and 16 percent of patients taking carbimazole. Thirty percent of patients who had previously received antithyroid drugs but were no longer receiving them were positive as well. The clinical significance of these intriguing findings is not known.

Other rare side effects of antithyroid drugs are listed in Table 1.

USE OF ANTITHYROID DRUGS DURING PREGNANCY AND LACTATION

Thyrotoxicosis occurs in 1 of every 1000 to 2000 pregnancies.¹¹³ Because of its relative rarity, there are no prospective clinical trials comparing drug regimens. Nevertheless, an antithyroid drug should be started at the time of diagnosis, since thyrotoxicosis itself presents a risk to the mother and fetus. Propylthiouracil has been preferred in North America because it was reputed to cross the placenta minimally as compared with methimazole. However, recent studies suggest that propylthiouracil does, in fact, cross the placenta,^{114,115} and clinical data do not show any differences in thyroid function at birth between fetuses exposed to propylthiouracil as compared with those exposed to methimazole.^{116,117}

In North America, propylthiouracil remains the treatment of choice during pregnancy, because congenital anomalies have been reported with methimazole, particularly aplasia cutis, usually described as single or multiple lesions of 0.5 to 3 cm at the vertex or occipital area of the scalp. This anomaly occurs spontaneously in 1 of 2000 births, but the frequency of this occurrence in association with methimazole use is not known.¹¹⁸ The use of methimazole is also associated with a very rare teratogenic syndrome termed "methimazole embryopathy," which is characterized by choanal or esophageal atresia.¹¹⁹ In a recent report, these anomalies occurred in 2 of 241 children of women exposed to methimazole, as compared with the spontaneous rate of 1 in 2500 to 1 in 10,000 for esophageal atresia and choanal atresia, respectively.¹¹⁹ In contrast, however, another study found no increase in the frequency of congenital abnormalities, including aplasia cutis, among 243 infants who were exposed to methimazole in utero¹²⁰; however, only external anomalies were reported. There has been at least one case of choanal atresia in an infant exposed to propylthiouracil.¹²¹

Because of the lack of availability of propylthiouracil in many countries, methimazole (or carbimazole) is still widely used in pregnancy. However, pregnant women should be treated with propylthiouracil when the drug is available. In the event of allergy to propylthiouracil, methimazole can be substituted. The Food and Drug Administration has categorized both propylthiouracil and methimazole as class D agents (i.e., drugs with strong evi-

Table 1. Side Effects of Antithyroid Drugs.*

Side Effect	Estimated Frequency	Comments
Minor		
Skin reactions	4–6%	Urticarial or macular reactions
Arthralgias	1–5%	May be harbinger of more severe arthritis
Gastrointestinal effects	1–5%	Includes gastric distress and nausea
Abnormal sense of taste or smell	Rare	With methimazole only
Sialadenitis	Very rare	Methimazole
Major		
Polyarthritis	1–2%	So-called antithyroid arthritis syndrome
ANCA-positive vasculitis	Rare	ANCA positivity is seen in patients with untreated Graves' disease and in asymptomatic persons who are taking antithyroid drugs, especially propylthiouracil
Agranulocytosis	0.1–0.5%	Mild granulocytopenia may be seen in patients with Graves' disease; may be more common with propylthiouracil ⁷⁷
Other hematologic side effects	Very rare	May include thrombocytopenia and aplastic anemia
Immunoallergic hepatitis	0.1–0.2%; 1% in some series ⁹⁷	Almost exclusively in patients taking propylthiouracil; a transient increase in aminotransferase levels is seen in 30% of patients taking propylthiouracil
Cholestasis	Rare	Exclusively with methimazole and carbimazole
Hypoprothrombinemia	Rare	No case reports since 1982 ¹¹⁰ ; only with propylthiouracil
Hypoglycemia	Rare	So-called insulin-autoimmune syndrome, which is seen mainly in Asian patients receiving sulfonyl-containing drugs; only with methimazole ¹¹¹
Pancreatitis	Very rare	One case report ¹¹²

* Data are from Cooper.⁷⁷ ANCA denotes antineutrophil cytoplasmic antibody.

dence of risk to the fetus) because of the potential for fetal hypothyroidism.

Once the thyrotoxicosis has come under control, the dose of antithyroid drug should be minimized to prevent fetal hypothyroidism. If the maternal free thyroxine serum level is maintained at or slightly above the upper limit of normal, the risk of fetal hypothyroidism is negligible.¹²² Even if fetal thyroid effects do occur, they are likely to be mild,¹²¹ and follow-up studies of children exposed in utero have not shown developmental or intellectual im-

pairment.^{123,124} By the third trimester, approximately 30 percent of women can discontinue antithyroid-drug therapy altogether and still remain euthyroid.¹²⁵

For nursing mothers, both antithyroid drugs are considered safe. Both appear in breast milk (methimazole more than propylthiouracil)¹¹³ but in low concentrations. Clinical studies of breast-fed infants have shown normal thyroid function^{126,127} and normal subsequent intellectual development in exposed infants.¹²⁸ Both drugs are approved for nursing mothers by the American Academy of Pediatrics.¹²⁹

THYROID STORM

An in-depth discussion about the management of thyroid storm, a sudden and dangerous increase in the symptoms and signs of thyrotoxicosis, is beyond the scope of this review. However, antithyroid-drug therapy plays a major role in the management of this syndrome. Although propylthiouracil is traditionally preferred because of its effects

on the conversion of thyroxine to triiodothyronine, there is no evidence that it is more efficacious than methimazole. A high dose of either drug should be used, namely 60 to 120 mg of methimazole or 600 to 1200 mg of propylthiouracil per day (both drugs given in divided doses). If necessary, both drugs can be given rectally,^{130,131} and there are case reports of intravenous administration of methimazole.¹³²

SUMMARY

Six decades after their introduction, antithyroid drugs continue to be important in the management of hyperthyroidism. Patients with Graves' disease, who have an approximately 40 to 50 percent chance of remission after 12 to 18 months of therapy, are the best candidates. Antithyroid drugs are deceptively easy to use, but because of the variability in the response of patients and the potentially serious side effects, all practitioners who prescribe the drugs need to have a working knowledge of their complex pharmacology.

REFERENCES

- Solomon B, Glinoe D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. *J Clin Endocrinol Metab* 1990;70:1518-24.
- Wartofsky L, Glinoe D, Solomon B, et al. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. *Thyroid* 1991;1:129-35.
- Cooper DS. Antithyroid drugs in the management of patients with Graves' disease: an evidence-based approach to therapeutic controversies. *J Clin Endocrinol Metab* 2003;88:3474-81.
- Idem*. Antithyroid drugs. *N Engl J Med* 1984;311:1353-62.
- Marchant B, Alexander WD, Robertson JWK, Lazarus JH. Concentration of 35S-propylthiouracil by the thyroid gland and its relationship to anion trapping mechanism. *Metabolism* 1971;20:989-99.
- Davidson B, Soodak M, Neary JT, et al. The irreversible inactivation of thyroid peroxidase by methylmercaptoimidazole, thiouracil, and propylthiouracil in vitro and its relationship to in vivo findings. *Endocrinology* 1978;103:871-82.
- Taurog A. Hormone synthesis and secretion. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's the thyroid: a fundamental and clinical text*. Philadelphia: Lippincott-Raven, 1996:47-80.
- McGregor AM, Petersen MM, McLachlan SM, Rooke P, Smith BR, Hall R. Carbimazole and the autoimmune response in Graves' disease. *N Engl J Med* 1980;303:302-7.
- Sonnet E, Massart C, Gibassier J, Allanic H, Maugendre D. Longitudinal study of soluble intercellular adhesion molecule-1 (ICAM-1) in sera of patients with Graves' disease. *J Endocrinol Invest* 1999;22:430-5.
- Tsatsoulis A, Vlachoyiannopoulos PG, Dalekos GN, Johnson EO, Moutsopoulos HM. Increased serum interleukin-1 beta during treatment of hyperthyroidism with antithyroid drugs. *Eur J Clin Invest* 1995;25:654-8. [Erratum, *Eur J Clin Invest* 1996;26:341.]
- Salvi M, Girasole G, Pedrazzoni M, et al. Increased serum concentrations of interleukin-6 (IL-6) and soluble IL-6 receptor in patients with Graves' disease. *J Clin Endocrinol Metab* 1996;81:2976-9.
- Mitsiades N, Poulaki V, Tseleni-Balafouta S, Chrousos GP, Koutas DA. Fas ligand expression in thyroid follicular cells from patients with thionamide-treated Graves' disease. *Thyroid* 2000;10:527-32.
- Zantut-Wittmann DE, Tambascia MA, da Silva Trevisan JA, Pinto GA, Vassallo J. Antithyroid drugs inhibit in vivo HLA-DR expression in thyroid follicular cells in Graves' disease. *Thyroid* 2001;11:575-80.
- Totterman TH, Karlsson FA, Bengtsson M, Mendel-Hartvig I. Induction of circulating activated suppressor-like T cells by methimazole therapy for Graves' disease. *N Engl J Med* 1987;316:15-22.
- Wang PW, Luo SF, Huang BY, Lin JD, Huang MJ. Depressed natural killer activity in Graves' disease and during antithyroid medication. *Clin Endocrinol (Oxf)* 1988;28:205-14.
- Corrales JJ, Lopez A, Ciudad J, Mories MT, Miralles JM, Orfao A. Methimazole therapy in Graves' disease influences the abnormal expression of CD69 (early activation antigen) on T cells. *J Endocrinol* 1997;155:491-500.
- Volpe R. The immunomodulatory effects of anti-thyroid drugs are mediated via actions on thyroid cells, affecting thyrocyte-immunocyte signalling: a review. *Curr Pharm Des* 2001;7:451-60.
- Davies TF, Weiss I, Gerber MA. Influence of methimazole on murine thyroiditis: evidence for immunosuppression in vivo. *J Clin Invest* 1984;73:397-404.
- Reinhardt W, Appel MC, Alex S, Yang YN, Braverman LE. The inhibitory effect of large doses of methimazole on iodine induced lymphocytic thyroiditis and serum anti-thyroglobulin antibody titers in BB/Wor rats. *J Endocrinol Invest* 1989;12:559-63.
- Wilson R, McKillop JH, Pearson C, Burnett AK, Thomson JA. Differential immunosuppressive action of carbimazole and propylthiouracil. *Clin Exp Immunol* 1988;73:312-5.
- Cooper DS, Saxe VC, Meskeel M, Maloof F, Ridgway EC. Acute effects of propylthiouracil (PTU) on thyroidal iodide organification and peripheral iodothyronine deiodination: correlation with serum PTU levels measured by radioimmunoassay. *J Clin Endocrinol Metab* 1982;54:101-7.
- Cooper DS, Bode HH, Nath B, Saxe V, Maloof F, Ridgway EC. Methimazole pharmacology in man: studies using a newly

- developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984;58:473-9.
23. Barnes HV, Bledsoe T. A simple test for selecting the thioamide schedule in thyrotoxicosis. *J Clin Endocrinol Metab* 1972;35:250-5.
24. Jansson R, Dahlberg PA, Johansson H, Lindstrom B. Intrathyroidal concentrations of methimazole in patients with Graves' disease. *J Clin Endocrinol Metab* 1983;57:129-32.
25. McCrudden DC, Hilditch TE, Connell JMC, McLellan AR, Robertson J, Alexander WD. Duration of antithyroid action of methimazole estimated with an intravenous perchlorate discharge test. *Clin Endocrinol (Oxf)* 1987;26:33-9.
26. Mashio Y, Beniko M, Ikota A, Mizumoto H, Kunita H. Treatment of hyperthyroidism with a small single daily dose of methimazole. *Acta Endocrinol (Copenh)* 1988;119:139-44.
27. Nicholas WC, Fischer RG, Stevenson RA, Bass JD. Single daily dose of methimazole compared to every 8 hours propylthiouracil in the treatment of hyperthyroidism. *South Med J* 1995;88:973-6.
28. Hoffman WH, Miceli JN. Pharmacokinetics of propylthiouracil in children and adolescents with Graves' disease in the hyperthyroid and euthyroid states. *Dev Pharmacol Ther* 1988;11:73-81.
29. Kampmann JP, Mortensen HB, Bach B, Waldorff S, Kristensen MB, Hansen JM. Kinetics of propylthiouracil in the elderly. *Acta Med Scand Suppl* 1979;624:93-8.
30. Jansson R, Lindstrom B, Dahlberg PA. Pharmacokinetic properties and bioavailability of methimazole. *Clin Pharmacokinet* 1985;10:443-50.
31. Cooper DS, Steigerwalt S, Migdal S. Pharmacology of propylthiouracil in thyrotoxicosis and chronic renal failure. *Arch Intern Med* 1987;147:785-6.
32. Giles HG, Roberts EA, Orrego H, Sellers EM. Determination of free propylthiouracil clearance and single sample prediction of steady state. *J Pharm Pharmacol* 1982;34:62-4.
33. Tallstedt L, Lundell G, Torring O, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. *N Engl J Med* 1992;326:1733-8.
34. Torring O, Tallstedt L, Wallin G, et al. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine — a prospective, randomized study. *J Clin Endocrinol Metab* 1996;81:2986-93.
35. Ljunggren JG, Torring O, Wallin G, et al. Quality of life aspects and costs in treatment of Graves' hyperthyroidism with antithyroid drugs, surgery, or radioiodine: results from a prospective, randomized study. *Thyroid* 1998;8:653-9.
36. Andrade VA, Gross JL, Maia AL. Effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective randomized study. *J Clin Endocrinol Metab* 2001;86:3488-93.
37. Nakazato N, Yoshida K, Mori K, et al. Antithyroid drugs inhibit radioiodine-induced increases in thyroid autoantibodies in hyperthyroid Graves' disease. *Thyroid* 1999;9:775-9.
38. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism: Standards of Care Committee, American Thyroid Association. *JAMA* 1995;273:808-12.
39. Kallner G, Vitols S, Ljunggren JG. Comparison of standardized initial doses of two antithyroid drugs in the treatment of Graves' disease. *J Intern Med* 1996;239:525-9.
40. Homsanit M, Sriussadaporn S, Vannasaeng S, Peerapatdit T, Nitiyanan W, Vichayanrat A. Efficacy of single daily dosage of methimazole vs. propylthiouracil in the induction of euthyroidism. *Clin Endocrinol (Oxf)* 2001;54:385-90.
41. He CT, Hsieh AT, Pei D, et al. Comparison of single daily dose of methimazole and propylthiouracil in the treatment of Graves' hyperthyroidism. *Clin Endocrinol (Oxf)* 2004;60:676-81.
42. DestinationRx home page. (Accessed January 13, 2005, at <http://www.destinationrx.com>.)
43. Reinwein D, Benker G, Lazarus JH, Alexander WD. A prospective randomized trial of antithyroid drug dose in Graves' disease therapy. *J Clin Endocrinol Metab* 1993;76:1516-21.
44. Page SR, Sheard CE, Herbert M, Hopton M, Jeffcoat WJ. A comparison of 20 or 40 mg per day of carbimazole in the initial treatment of hyperthyroidism. *Clin Endocrinol (Oxf)* 1996;45:511-6. [Erratum, *Clin Endocrinol (Oxf)* 1997;46:240.]
45. Hegedüs L, Hansen JM, Bech K, et al. Thyroid stimulating immunoglobulins in Graves' disease with goitre growth, low thyroxine and increasing triiodothyronine during PTU treatment. *Acta Endocrinol (Copenh)* 1984;107:482-8.
46. Schleusener H, Schwander J, Fischer C, et al. Prospective multicentre study on the prediction of relapse after antithyroid drug treatment in patients with Graves' disease. *Acta Endocrinol (Copenh)* 1989;120:689-701. [Erratum, *Acta Endocrinol (Copenh)* 1989;121:304.]
47. Vitti P, Rago T, Chiovato L, et al. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. *Thyroid* 1997;7:369-75.
48. Benker G, Rienwein D, Kahaly G, et al. Is there a methimazole dose effect on remission rate in Graves' disease? Results from a long-term prospective study. *Clin Endocrinol (Oxf)* 1998;49:451-7.
49. Michelangeli V, Poon C, Taft J, Newnham H, Topliss D, Colman P. The prognostic value of thyrotropin receptor antibody measurement in the early stages of treatment of Graves' disease with antithyroid drugs. *Thyroid* 1998;8:119-24.
50. Fukao A, Takamatsu J, Murakami Y, et al. The relationship of psychological factors to the prognosis of hyperthyroidism in antithyroid drug-treated patients with Graves' disease. *Clin Endocrinol (Oxf)* 2003;58:550-5.
51. Feldt-Rasmussen U, Schleusener H, Carayon P. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long-term remission after medical therapy of Graves' disease. *J Clin Endocrinol Metab* 1994;78:98-102.
52. Schott M, Morgenthaler NG, Fritzen R, et al. Levels of autoantibodies against human TSH receptor predict relapse of hyperthyroidism in Graves' disease. *Horm Metab Res* 2004;36:92-6.
53. Nedrebo BG, Holm PI, Uhlving S, et al. Predictors of outcome and comparison of different drug regimens for the prevention of relapse in patients with Graves' disease. *Eur J Endocrinol* 2002;147:583-9.
54. Teng CS, Yeung RTT. Changes in thyroid-stimulating antibody activity in Graves' disease treated with antithyroid drug and its relationship to relapse: a prospective study. *J Clin Endocrinol Metab* 1980;50:144-7.
55. Werner RS, Romaldini JH, Farah CS, Werner MC, Bromberg N. Serum thyroid stimulating antibody, thyroglobulin levels, and thyroid suppressibility measurement as predictors of the outcome of combined methimazole and triiodothyronine therapy in Graves' disease. *Thyroid* 1991;1:293-9.
56. Jorde R, Ytre-Arne K, Stormer J, Sundsfjord J. Short-term treatment of Graves' disease with methimazole in high versus low doses. *J Intern Med* 1995;238:161-5.
57. Wilson R, Buchanan L, Fraser WD, McKippop JH, Thomsen JA. Do higher doses of carbimazole improve remission in Graves' disease? *QJM* 1996;89:381-5.
58. Grebe SKG, Feek CM, Ford HC, et al. A randomized trial of short-term treatment of Graves' disease with high-dose carbimazole plus thyroxine versus low-dose carbimazole. *Clin Endocrinol (Oxf)* 1998;48:585-92.
59. Paschke R, Vogg M, Kristoferitsch R, et al. Methimazole has no dose-related effect on the intensity of the intrathyroidal autoimmune process in relapsing Graves' disease. *J Clin Endocrinol Metab* 1995;80:2470-4.
60. Allannic H, Fauchet R, Orgiazzi J, et al. Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. *J Clin Endocrinol Metab* 1990;70:675-9.
61. Garcia-Mayor RVG, Paramo C, LunaCano R, Perez Mendez LF, Galofre JC, Andrade A. Antithyroid drug and Graves' hyperthyroidism: significance of treatment duration and TRAb determination on lasting remission. *J Endocrinol Invest* 1992;15:815-20.
62. Maugendre D, Gatel A, Campion L, et al. Antithyroid drugs and Graves' disease — prospective randomized assessment of long-term treatment. *Clin Endocrinol (Oxf)* 1999;50:127-32.

63. Abraham P, Avenell A, Watson WA, Park CM, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. *Cochrane Database Syst Rev* 2004;2:CD003420.
64. Slingerland DW, Burrows BA. Long-term antithyroid treatment in hyperthyroidism. *JAMA* 1979;242:2408-10.
65. Hashizume K, Ichikawa I, Sakurai A, et al. Administration of thyroxine in treated Graves' disease: effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. *N Engl J Med* 1991;324:947-53.
66. McIver B, Rae P, Beckett G, Wilkinson E, Gold A, Toft A. Lack of effect of thyroxine in patients with Graves' hyperthyroidism who are treated with an antithyroid drug. *N Engl J Med* 1996;334:220-4.
67. Rittmaster RS, Zwicker H, Abbott EC, et al. Effect of methimazole with or without exogenous L-thyroxine on serum concentrations of thyrotropin (TSH) receptor antibodies in patients with Graves' disease. *J Clin Endocrinol Metab* 1996;81:3283-8.
68. Pfeilschifter J, Zeigler R. Suppression of serum thyrotropin with thyroxine in patients with Graves' disease: effects on recurrence of hyperthyroidism and thyroid volume. *Eur J Endocrinol* 1997;136:81-6.
69. Cho BY, Shong MH, Yi KH, Lee HK, Koh CS, Min HK. Evaluation of serum basal thyrotrophin levels and thyrotrophin receptor antibody activities as prognostic markers for discontinuation of antithyroid drug treatment in patients with Graves' disease. *Clin Endocrinol (Oxf)* 1992;36:585-90.
70. Hedley AJ, Young RE, Jones SJ, Alexander WD, Bewsher PD. Antithyroid drugs in the treatment of hyperthyroidism of Graves' disease: long-term follow-up of 434 patients. *Clin Endocrinol (Oxf)* 1989;31:209-18.
71. Berglund J, Christensen SB, Dymling JF, Hallengren B. The incidence of recurrence and hypothyroidism following treatment with antithyroid drugs, surgery or radioiodine in all patients with thyrotoxicosis in Malmö during the period 1970-1974. *J Intern Med* 1991;229:435-42.
72. Amino N, Tanizawa O, Mori H, et al. Aggravation of thyrotoxicosis in early pregnancy and after delivery in Graves' disease. *J Clin Endocrinol Metab* 1982;55:108-12.
73. Wood LC, Ingbar SH. Hypothyroidism as a late sequela in patient with Graves' disease treated with antithyroid agents. *J Clin Invest* 1979;64:1429-36.
74. Braga M, Walpert N, Burch HB, Solomon BL, Cooper DS. The effect of methimazole on cure rates after radioiodine treatment for Graves' hyperthyroidism: a randomized clinical trial. *Thyroid* 2002;12:135-9.
75. Santos RB, Romaldini JH, Ward LS. Propylthiouracil reduces the effectiveness of radioiodine treatment in hyperthyroid patients with Graves' disease. *Thyroid* 2004;14:525-30.
76. Bonnema SJ, Bønbæk FN, Vejse A, Marving J, Hegedus L. Propylthiouracil before ¹³¹I therapy of hyperthyroid disease: effect on cure rate evaluated by a randomized clinical trial. *J Clin Endocrinol Metab* 2004;89:4439-44.
77. Cooper DS. The side effects of antithyroid drugs. *Endocrinologist* 1999;9:457-76.
78. Ducornet B, Duprey J. Effets secondaires des antithyroïdiens de synthèse. *Ann Med Interne* 1988;139:410-31.
79. Meyer-Gessner M, Benker G, Olbricht T, et al. Nebenwirkungen der antithyroïdalen Therapie der Hyperthyreose. *Dtsch Med Wochenschr* 1989;114:166-71.
80. Shabtai R, Shapiro MS, Orenstein D, Taragan R, Shenkman L. The antithyroid arthritis syndrome reviewed. *Arthritis Rheum* 1984;27:227-9.
81. Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: special reference to normal white blood cell count agranulocytosis. *Thyroid* 2004;14:459-62.
82. Pearce SH. Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. *Clin Endocrinol (Oxf)* 2004;61:589-94.
83. Toth EL, Mant MJ, Shivji S, Ginsberg J. Propylthiouracil-induced agranulocytosis: an unusual presentation and a possible mechanism. *Am J Med* 1988;85:725-7.
84. Berkman EM, Orlin JB, Wolfson J. An anti-neutrophil antibody associated with a propylthiouracil-induced lupus-like syndrome. *Transfusion* 1983;23:135-8.
85. Fibbe WE, Claas FHJ, Van der Star-Dijkstra W, Schaafsma MR, Meyboom RH, Falkenburg JH. Agranulocytosis induced by propylthiouracil: evidence of a drug dependent antibody reacting with granulocytes, monocytes and haematopoietic progenitor cells. *Br J Haematol* 1986;64:363-73.
86. Akamizu T, Ozaki S, Hiratani H, et al. Drug-induced neutropenia associated with anti-neutrophil cytoplasmic antibodies (ANCA): possible involvement of complement in granulocyte cytotoxicity. *Clin Exp Immunol* 2002;127:92-8.
87. Tajiri J, Noguchi S, Murakami N. Usefulness of granulocyte count measurement four hours after injection of granulocyte colony-stimulating factor for detecting recovery from antithyroid drug-induced granulocytopenia. *Thyroid* 1997;7:575-8.
88. Cooper DS. Antithyroid drugs for the treatment of hyperthyroidism caused by Graves' disease. *Endocrinol Metab Clin North Am* 1998;27:225-47.
89. Vanderpump MP, Ahlquist JA, Franklyn JA, Clayton RN. Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism: the Research Unit of the Royal College of Physicians of London, the Endocrinology and Diabetes Committee of the Royal College of Physicians of London, and the Society for Endocrinology. *BMJ* 1996;313:539-44.
90. Sheng WH, Hung CC, Chen YC, et al. Antithyroid-drug-induced agranulocytosis complicated by life-threatening infections. *QJM* 1999;92:455-61.
91. Andres E, Kurtz JE, Perrin AE, Dufour P, Schlienger JL, Maloisel F. Haematopoietic growth factor in antithyroid-drug-induced agranulocytosis. *QJM* 2001;94:423-8.
92. Julia A, Olona M, Bueno J, et al. Drug-induced agranulocytosis: prognostic factors in a series of 168 episodes. *Br J Haematol* 1991;79:366-71.
93. Tajiri J, Noguchi S, Okamura S, et al. Granulocyte colony-stimulating factor treatment of antithyroid drug-induced granulocytopenia. *Arch Intern Med* 1993;153:509-14.
94. Fukata S, Kuma K, Sugawara M. Granulocyte colony-stimulating factor (G-CSF) does not improve recovery from antithyroid drug-induced agranulocytosis: a prospective study. *Thyroid* 1999;9:29-31.
95. Liaw Y-F, Huang M-J, Fan K-D, Li K-L, Wu S-S, Chen T-J. Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. *Ann Intern Med* 1993;118:424-8.
96. Gurlek A, Cobaukara V, Bayraktar M. Liver tests in hyperthyroidism: effect of antithyroid therapy. *J Clin Gastroenterol* 1997;24:180-3.
97. Williams KV, Nayak S, Becker D, Reyes J, Burmeister LA. Fifty years of experience with propylthiouracil-associated hepatotoxicity: what have we learned? *J Clin Endocrinol Metab* 1997;82:1727-33.
98. Ruiz JK, Rossi GV, Vallejos HA, Brenet RW, Lopez IB, Escobano AA. Fulminant hepatic failure associated with propylthiouracil. *Ann Pharmacother* 2003;37:224-8.
99. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl* 2004;10:1018-23.
100. Arab DM, Malatjalian DA, Rittmaster RS. Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 1995;80:1083-5.
101. Parker WA. Propylthiouracil-induced hepatotoxicity. *Clin Pharm* 1982;1:471-4.
102. Horton RC, Sheppard MC, Emery P. Propylthiouracil-induced systemic lupus erythematosus. *Lancet* 1989;2:568.
103. Gunton JE, Stiel J, Caterson RJ, McElduff A. Anti-thyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis: a case report and review of the literature. *J Clin Endocrinol Metab* 1999;84:13-6.
104. Sera N, Ashizawa K, Ando T, et al. Treatment with propylthiouracil is associated with appearance of antineutrophil cytoplasmic antibodies in some patients with Graves' disease. *Thyroid* 2000;10:595-9.
105. Case Records of the Massachusetts General Hospital (Case 21-2002.) *N Engl J Med* 2002;347:122-30.
106. Waldhauser L, Uetrecht J. Oxidation of propylthiouracil to reactive metabolites by activated neutrophils: implications for agranulocytosis. *Drug Metab Dispos* 1991;19:354-9.
107. Sato H, Hattori M, Fujieda M, et al. High prevalence of antineutrophil cytoplasmic antibody positivity in childhood onset

- Graves' disease treated with propylthiouracil. *J Clin Endocrinol Metab* 2000;85:4270-3.
108. Guma M, Salinas I, Reverter JL, et al. Frequency of antineutrophil cytoplasmic antibody in Graves' disease patients treated with methimazole. *J Clin Endocrinol Metab* 2003;88:2141-6.
 109. Harper L, Chin L, Daykin J, et al. Propylthiouracil and carbimazole associated-antineutrophil cytoplasmic antibodies (ANCA) in patients with Graves' disease. *Clin Endocrinol (Oxf)* 2004;60:671-5.
 110. Ikeda S, Schweiss JF. Excessive blood loss during operation in the patient treated with propylthiouracil. *Can Anaesth Soc J* 1982;29:477-80.
 111. Uchigata Y, Eguchi Y, Takayama-Hasumi S, Omori Y. Insulin autoimmune syndrome (Hirata disease): clinical features and epidemiology in Japan. *Diabetes Res Clin Pract* 1994;22:89-94.
 112. Taguchi M, Yokota M, Koyano H, Endo Y, Ozawa Y. Acute pancreatitis and parotitis induced by methimazole in a patient with Graves' disease. *Clin Endocrinol (Oxf)* 1999;51:667-70.
 113. Mandel SJ, Cooper DS. The use of antithyroid drugs in pregnancy and lactation. *J Clin Endocrinol Metab* 2001;86:2354-9.
 114. Gardner DF, Cruikshank DP, Hays PM, Cooper DS. Pharmacology of propylthiouracil (PTU) in pregnant hyperthyroid women: correlation of maternal PTU concentrations with cord serum thyroid function tests. *J Clin Endocrinol Metab* 1986;62:217-20.
 115. Mortimer RH, Cannell GR, Addison RS, Johnson LP, Roberts MS, Bernus I. Methimazole and propylthiouracil equally cross the perfused human term placental lobule. *J Clin Endocrinol Metab* 1997;82:3099-102.
 116. Momotani N, Noh JY, Ishikawa N, Ito K. Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism. *J Clin Endocrinol Metab* 1997;82:3633-6.
 117. Wing DA, Millar LK, Koonings PP, Montoro MN, Mestman JH. A comparison of propylthiouracil and methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol* 1994;170:90-5.
 118. Mandel SJ, Brent GA, Larsen PR. Review of antithyroid drug use during pregnancy and report of a case of aplasia cutis. *Thyroid* 1994;4:129-33.
 119. Di Gianantonio E, Schaefer C, Mastroiacovo PP, et al. Adverse effects of prenatal methimazole exposure. *Teratology* 2001;64:262-6.
 120. Momotani N, Ito K, Hamada N, Ban Y, Nishikawa Y, Mimura T. Maternal hyperthyroidism and congenital malformation in the offspring. *Clin Endocrinol (Oxf)* 1984;20:695-700.
 121. Cheron RG, Kaplan MM, Larsen PR, Selenkow HA, Crigler JF Jr. Neonatal thyroid function after propylthiouracil therapy for maternal Graves' disease. *N Engl J Med* 1981;304:525-8.
 122. Momotani N, Noh J, Oyanagi H, Ishikawa N, Ito K. Antithyroid drug therapy for Graves' disease during pregnancy: optimal regimen for fetal thyroid status. *N Engl J Med* 1986;315:24-8.
 123. Messer PM, Hauffa BP, Olbricht T, Benker G, Kotulla P, Reinwein D. Antithyroid drug treatment of Graves' disease in pregnancy: long-term effects on somatic growth, intellectual development and thyroid function of the offspring. *Acta Endocrinol (Copenh)* 1990;123:311-6.
 124. Eisenstein Z, Weiss M, Katz Y, Bank H. Intellectual capacity of subjects exposed to methimazole or propylthiouracil in utero. *Eur J Pediatr* 1992;151:558-9.
 125. Hamburger JL. Diagnosis and management of Graves' disease in pregnancy. *Thyroid* 1992;2:219-24.
 126. Momotani N, Yamashita R, Makino E, Noh JY, Ishikawa N, Ito K. Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol (Oxf)* 2000;53:177-81.
 127. Azizi F, Hedayati M. Thyroid function in breast-fed infants whose mothers take high doses of methimazole. *J Endocrinol Invest* 2002;25:493-6.
 128. Azizi F, Bahrainian M, Khamseh ME, Khoshniat M. Intellectual development and thyroid function in children who were breast-fed by thyrotoxic mothers taking methimazole. *J Pediatr Endocrinol Metab* 2003;16:1239-43.
 129. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics* 2001;108:776-89.
 130. Jongjaroenprasert W, Akarawut W, Chantasart D, Chailurkit L, Rajatanavin R. Rectal administration of propylthiouracil in hyperthyroid patients: comparison of suspension enema and suppository form. *Thyroid* 2002;12:627-31.
 131. Nabil N, Miner DJ, Amatruda JM. Methimazole: an alternative route of administration. *J Clin Endocrinol Metab* 1982;54:180-1.
 132. Junik R, Sowinski J, Zamyshlowska H, Gembicki M. Effect of intravenous methimazole on serum levels of thyroid hormones in patients with hyperthyroidism resistant to oral thyrostatic drugs. *Endokrynol Pol* 1989;40:307-13. (In Polish.)

Copyright © 2005 Massachusetts Medical Society.

POWERPOINT SLIDES OF JOURNAL FIGURES AND TABLES

At the *Journal's* Web site, subscribers can automatically create PowerPoint slides of *Journal* figures and tables. Click on a figure or table in the full-text version of any article at www.nejm.org, and then click on PowerPoint Slide for Teaching. A PowerPoint slide containing the image, with its title and reference citation, can then be downloaded and saved.