REVIEW ARTICLE

DRUG THERAPY

Antithyroid Drugs

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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.

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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 1[9] 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 cells[14] 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 studies[20] 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 propylthiouracil[23] 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 methimazole[22] (but not propylthiouracil[32]) 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.

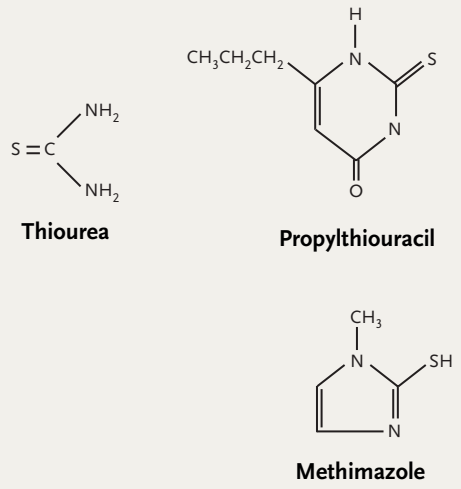


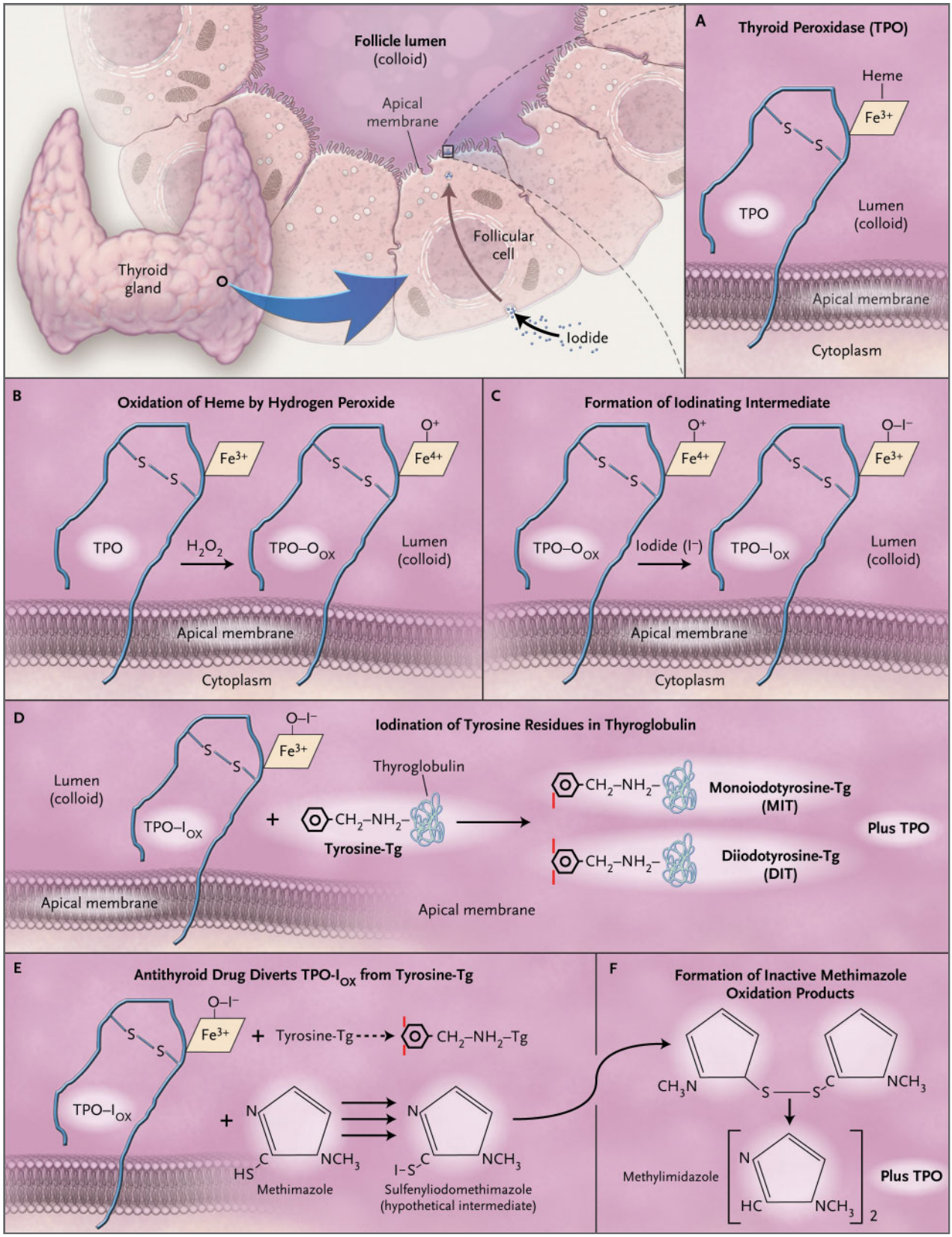
Figure 1. Chemical Structures of Propylthiouracil and Methimazole, as Compared with Thiourea.

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 disulfide[7] 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.



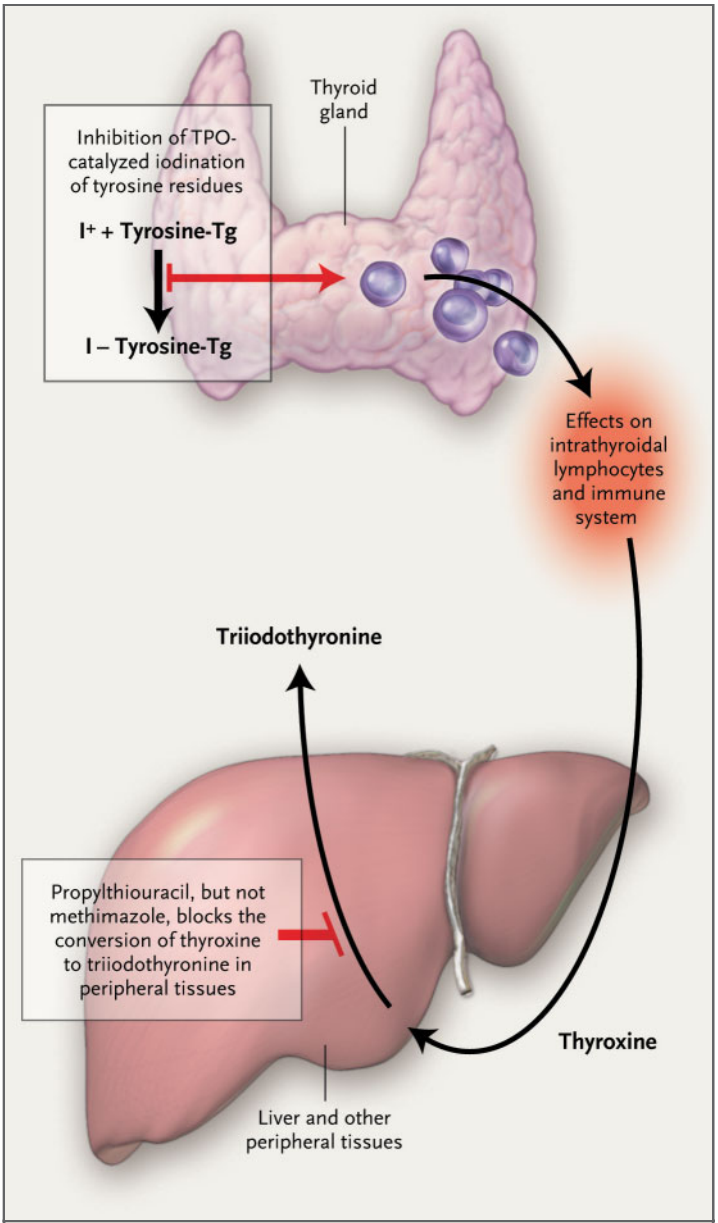


Figure 3. Effects of Antithyroid Drugs.

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.

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] 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 adherence[27] 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

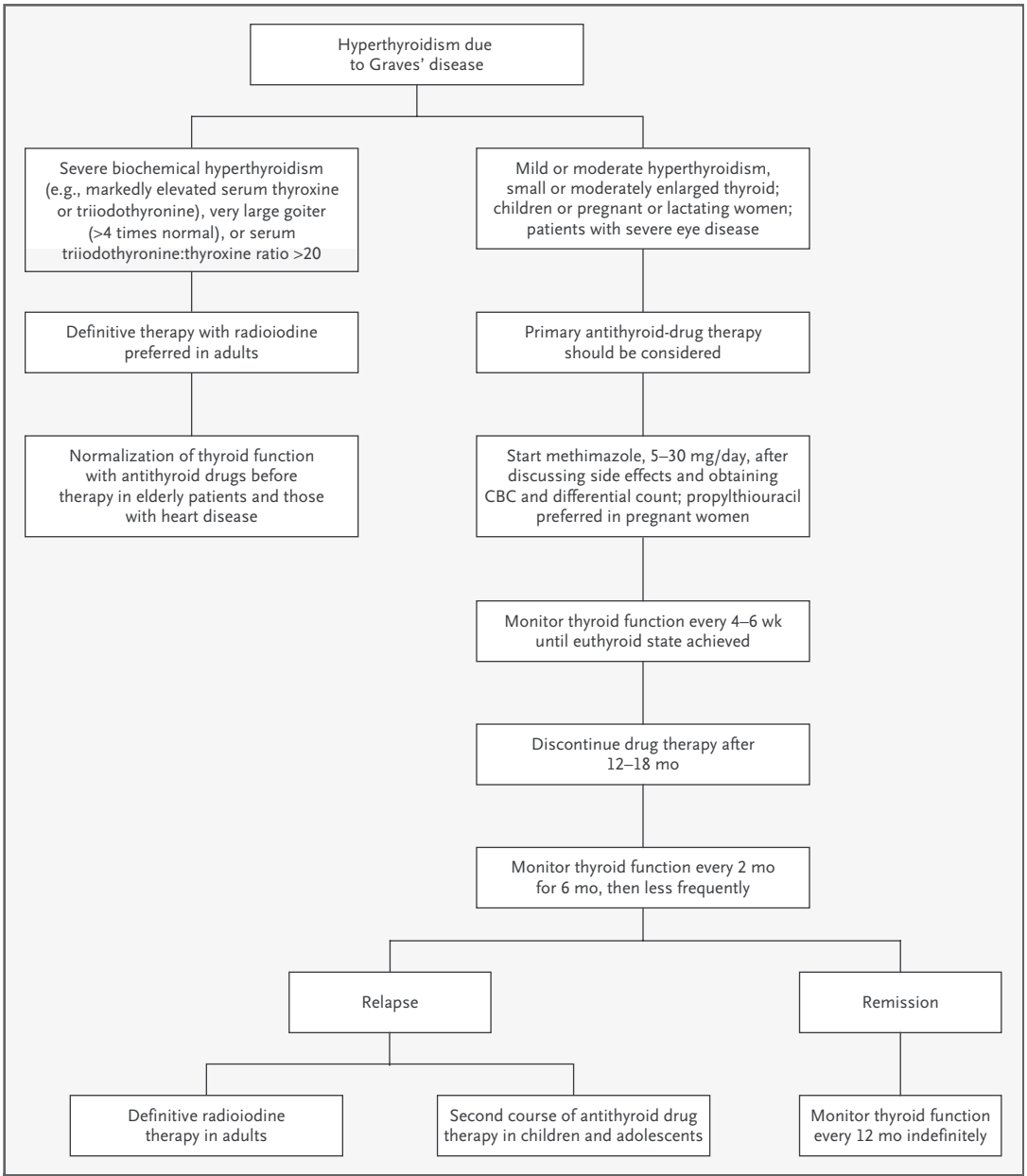


Figure 4. Algorithm for the Use of Antithyroid Drugs among Patients with Graves' Disease.

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 States[1] 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 differential 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 immunofluorescence[83] 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 cholestatic 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 utero[120]; 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 evidence 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-

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 sulfhydryl-containing drugs; only with methimazole[111]
Pancreatitis	Very rare	One case report[112]

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

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.

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