

THYROID TODAY

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ANTITHYROID DRUGS IN THE TREATMENT OF THYROTOXICOSIS

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Of the three commonly employed modalities for treating thyrotoxicosis (drugs, radioactive iodine, and surgery), antithyroid drugs are the least likely to induce permanent remission. They are nevertheless the most widely used form of therapy for this disease for two important reasons: (1) they do not produce permanent morbidity (hypothyroidism, hypoparathyroidism, etc); and (2) they do not require special skills, training, or licensing, and thus can be prescribed by general physicians.

Mechanism of Action

The antithyroid drugs commonly in use throughout the world are generically thionamides. All have an $=N-C=S$ configuration in the molecule. The two most commonly employed substances in the United States are propylthiouracil and methimazole, which have a six- and a five-membered ring structure, respectively. It is believed that thionamides act primarily by inhibiting thyroid peroxidase, an enzyme that catalyzes both the oxidation of iodide ion to a form in which it can be covalently bound into the tyrosyl residues in thyroglobulin within the lumen of the thyroid follicle and the "coupling" of iodotyrosyl residues in thyroglobulin to form thyroxine and triiodothyronine. The coupling reaction is much more sensitive to inhibition by thionamides. Thus, a complete remission of thyrotoxicosis can be induced by antithyroid drugs, even though a supranormal thyroid radioactive iodine uptake is maintained. The important point to remember is that thionamide drugs inhibit the iodination of thyroglobulin and the synthesis of thyroid hormone but

do not inhibit the thyroid iodide pump, which concentrates iodide in the thyroid cell, nor do they have any direct effect on the rate of secretion of preformed thyroid hormone stored within the thyroid follicles.

There is a large store of hormone within the thyroid gland, enough in a normal individual with a normal rate of secretion to maintain a euthyroid state for six to nine months, even if all synthesis of thyroid hormone is abolished. Therefore, an immediate return to a euthyroid state cannot be achieved in thyrotoxic patients treated solely with these drugs. Although patients with thyrotoxicosis usually have enlarged thyroids and a supranormal amount of stored hormone, their rate of secretion of thyroid hormone is greatly increased above normal. Thus, they have a fall of their plasma thyroid hormone concentration to a euthyroid range in an average of three months, a considerably more rapid rate of fall than can be achieved in normal individuals.

Choice of Patients

Although thionamides are effective in almost all thyrotoxic patients, their use is generally reserved for those with Graves' disease. Toxic nodular goiter (single or multiple) has a different pathogenesis and natural history than Graves' disease. The defect in toxic nodular goiter is one of localized intrathyroidal autonomy resulting in hypersecretion by one or more clonal groups of thyroid cells. Although antithyroid therapy can induce remission in patients with toxic nodules by inhibiting hormone synthesis, relapse almost invariably occurs when the drug administration is stopped because no basic change in the underlying autonomy has been produced.

The cause of Graves' disease is not known, although much evidence has accumulated over the last 20 years to suggest that it is an immunologic disorder of some type. The underlying problem is presumably an abnormal humoral thyroid stimulator that may be derived from lymphocytes. Not being able to treat the cause, one is compelled to treat the end organ from which the thyrotoxic manifestation is derived. The comforting feature of Graves' disease is that it has spontaneous cycles of remission and activity. If one treats the active phase of the disease with anti-

thyroid drugs, lasting, and sometimes permanent, remissions can be produced in approximately one third of all patients. Unfortunately, there is no way of predicting with certainty which patients will remain in remission. In most series, however, the patients with small goiters and relatively mild hyperthyroidism stand the best chance.

The lasting remission rates reported in various series over the last three decades have ranged from 14% to 96%, with a mean of 56%. There has been a general downward trend in the rate over the years, possibly related to occasional early overenthusiasm, since the scatter is wide (Fig. 1). The current mean is just under 40%.

Various tests have been proposed to determine which patients are likely to remain in remission when antithyroid therapy is discontinued. The two most commonly employed are the thyroid suppression test¹ (using triiodothyronine or thyroxine to suppress thyroid radioactive iodine or perchlorate uptake) and the thyrotropin-releasing hormone test² (measuring the rise in plasma thyrotropin level following a bolus intravenous injection of thyrotropin-releasing hormone). Both these tests give abnormal findings in patients with thyrotoxicosis; recovery of a normal response during antithyroid therapy indicates the patient is likely to remain in remission if the drug administration is stopped. However, the tests are quite expensive and inconvenient. They are also not completely reliable; after discontinuing antithyroid therapy, some patients with normal test results will relapse and some with abnormal results will remain in remission.^{3,4} The absence of thyroid-stimulating antibodies in the plasma at the time of drug withdrawal has also been espoused as a valuable prognosticator of lasting remission.⁵ However, this is an expensive research test of limited availability. I believe it is preferable to use the cheaper and more reliable test of simply stopping therapy at the appropriate time and observing the patient's course.

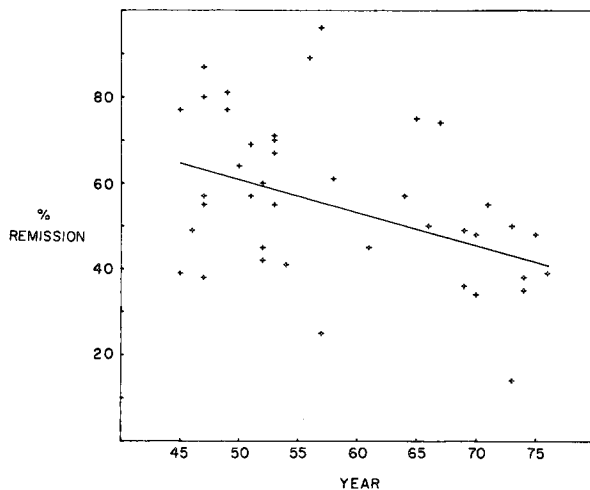


Figure 1
Remission rates after termination of antithyroid therapy according to year of publication of articles reviewed. The least-squares regression line for all plotted data from 1945 to 1976 is shown.⁹

The classic triad of Graves' disease includes a diffuse goiter, thyrotoxicosis, and exophthalmos. All three elements are often not present simultaneously, and sometimes only one ever becomes manifest during the lifetime of a patient. This treatise will be concerned only with the therapy of the thyrotoxicosis.

Patients of any age from birth to senility can be successfully treated with antithyroid drugs. However, since the thyroid-blocking effect of thionamides wears off within two to four days after interrupting therapy, compliance with the prescribed regimen is necessary. Because the dose may have to be adjusted in individual patients in the event of resistance to the drug or the development of hypothyroidism, patient cooperation in keeping follow-up appointments is also necessary. Unless one is certain that the patient will be unreliable in taking medication and returning for scheduled visits, antithyroid drugs are the best initial choice for a therapeutic trial. Patient unreliability is also a serious problem in the management of the hypothyroidism likely to result from treatment with radioactive iodine or surgery.

Individuals who have had two or more relapses following antithyroid drug therapy are unlikely to have a lasting remission following a further course. I believe such patients are best treated by alternative methods, preferably radioactive iodine. Antithyroid therapy is recommended most strongly for the "virgin" cases of thyrotoxicosis that have not previously been treated. Some clinicians think that elderly patients should be treated with radioactive iodine rather than drugs because the probability of lasting remission following cessation of drug therapy in such patients is very low. However, to my knowledge, there are no data indicating that elderly patients with Graves' disease are less likely than young patients to remain in remission. Thyrotoxicosis in elderly patients has been thought to be caused primarily by the development of autonomous hyperfunctioning nodules in a preexisting goiter. While this certainly does occur, thyrotoxic Graves' disease can develop for the first time in the eighth or ninth decade of life. I have seen two such patients in the last year, both of whom were successfully treated with thionamide therapy.

Dose and Frequency of Thionamide Administration

The relative potency of propylthiouracil and methimazole is not definitively established. Early data, employing acute suppression of radioactive iodine uptake as an index, suggested that methimazole was 100 times as potent as propylthiouracil.⁶ Subsequent clinical trials indicated that the potency ratio might be 10:1. The standard dose is 300 mg of propylthiouracil or 30 mg of methimazole daily. It is usually recommended that the drugs be given in three equal doses at eight-hour intervals because of their rapid metabolism. This is inconvenient, and compliance with an eight-hour schedule is particularly difficult to achieve with children. In spite of theoretical objections, I have found that in almost all patients, including those with severely toxic conditions, giving either propylthiouracil or methima-

zole once daily in the same total daily dose that would be used if the medication were given every eight hours induces a remission of the thyrotoxicosis as rapidly and effectively as giving divided doses.⁷ My colleagues and I have routinely used the single daily dose regimen in our clinic for the last 20 years. Only rarely have patients failed to respond to this program. In such patients, it is not clear that divided doses are more effective, since the drug-resistant patients are usually also refractory to divided daily doses.

Although we have not found it necessary in our clinic, the physician may be more comfortable prescribing antithyroid drugs on an every-eight-hours basis rather than a single daily dose regimen for severely thyrotoxic patients. The dose can be given once daily as soon as the patient shows definite improvement. A perchlorate discharge test (described below) has been recommended to identify those patients who will undergo satisfactory remission with single daily dose antithyroid therapy.⁸ I think that this test is unwarranted for at least three reasons: (1) essentially all patients respond satisfactorily to the single daily dose regimen; (2) the perchlorate test is expensive and time-consuming; and (3) the underlying rationale for employing the perchlorate test in this context is imprecise.

To amplify a bit on the last point, perchlorate is a monovalent anion of approximately the same size and shape as iodide and is a competitive inhibitor of the thyroid iodide pump. Any inorganic iodide present in the thyroid gland will thus be discharged when a large dose of perchlorate is given. The test is performed one to two hours after giving a tracer dose of radioactive iodide to a patient being treated with antithyroid drugs. In normal, untreated subjects, radioactive iodide entering the thyroid gland is organically bound to thyroglobulin within a few seconds. In the presence of fully inhibiting doses of thionamides, essentially all thyroid radioactive iodine will be present as inorganic iodide. This will be discharged from the gland by subsequent administration of perchlorate. However, as stated above under "Mechanism of Action," formation of thyroxine and triiodothyronine is inhibited by much smaller doses of thionamide drugs than is organic binding of iodine to thyroglobulin. It is inhibition of thyroid hormone synthesis that produces the remission. Thus, if the dose of thionamide is sufficient to inhibit thyroid hormone synthesis but insufficient to block organic binding of radioactive iodine into thyroglobulin, a patient may undergo a perfectly satisfactory remission even though no radioactive iodide is discharged from the gland by perchlorate.

Therapeutic Plan

Propylthiouracil and methimazole can be used interchangeably. In our clinic, however, my colleagues and I currently use methimazole because it is more potent and fewer pills are required for an average daily dose. The starting dose is 30 mg of methimazole given once daily. If there is no definite clinical or chemical improvement in six weeks, the dose is doubled to 60 mg of methimazole

once daily; otherwise, the same dose is continued. In those patients requiring a doubling of the dose, if no definite clinical or chemical improvement is seen in another six weeks (a total of 12 weeks of treatment), the patients are considered refractory to treatment with antithyroid drugs and are treated with radioactive iodine. We make an arbitrary decision of refractoriness at 12 weeks because too often in the past we have continued antithyroid therapy with patients who have not had an adequate response, thinking that they just need a little more time. Only after one to two years of treatment with large doses of antithyroid drugs have we realized that the patient still has inadequately treated hyperthyroidism. This has occurred in patients treated with either divided or single daily doses. Fortunately, only a very small number of patients are refractory to antithyroid therapy (probably less than 5%). There is no clear evidence that refractory patients will have a better response when antithyroid drugs are given in divided daily doses.

As soon as the patient becomes clinically and chemically euthyroid (which takes an average of about three months), thionamide therapy is stopped abruptly. Patients are reevaluated at monthly intervals for the first three months, three-month intervals for the next six months, and then annually for the remainder of their lifetimes. Patients are also told to return immediately if they think that a relapse is occurring. In our experience to date,⁹ approximately one third of the patients remain in remission for at least several years following short-term antithyroid therapy (Fig. 2). If a relapse occurs, antithyroid therapy is reinstated and continued for an additional year. Patients are seen at six-week intervals during that time to evaluate progress. At the end of the further year of therapy, the drug therapy is again stopped and the patient followed up as before. If a relapse occurs again, the patient is considered unlikely to have a lasting remission with thionamide therapy, and radioactive iodine is used as definitive treatment. Occasional patients prefer to have repeated or continual treatment with antithyroid drugs, or to have surgical therapy.

Hypothyroidism develops during treatment in approximately 10% of patients given standard doses of either propylthiouracil or methimazole. In addition to the usual symptoms of hypothyroidism, it is characteristic for the patient's thyroid to begin enlarging markedly because of the increase in thyrotropin secretion associated with reduced negative feedback from the pituitary when plasma thyroid hormone concentration drops below normal. If the hypothyroidism occurs during short-term therapy, the antithyroid drug therapy is stopped abruptly, as it would be if the patient had become euthyroid. No further antithyroid therapy is given unless the patient has a relapse. If hypothyroidism occurs during the long-term one-year therapy, we continue with the same dose of antithyroid drug rather than reducing it, since this dose is obviously effective in inhibiting the patient's thyroid hormone synthesis. We alle-

viate the hypothyroidism by "back-titrating" with 0.1 to 0.3 mg of levothyroxine sodium daily. Levothyroxine treatment will cause a regression of the thyroid enlargement that has developed during the hypothyroid phase, and the goiter will return to the preexisting size characteristic of the patient's Graves' disease.

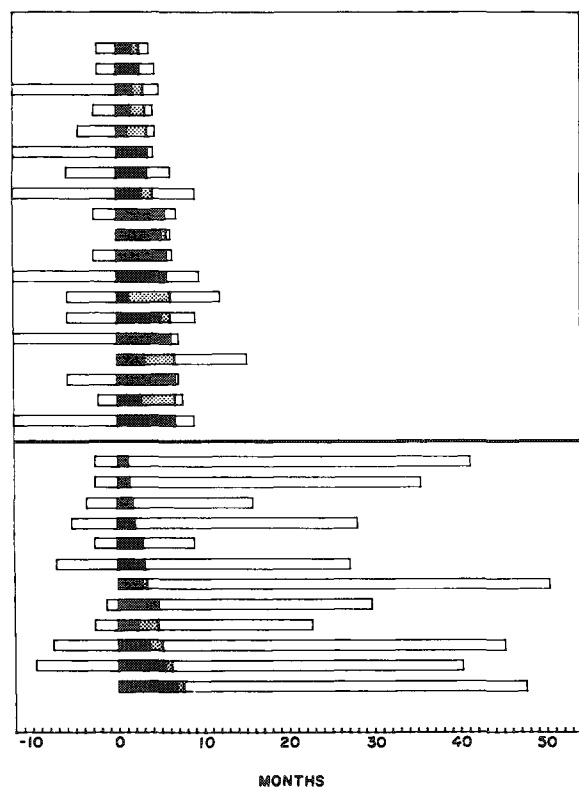


Figure 2
Course of previously untreated patients with Graves' disease given short-term antithyroid therapy. Top portion shows relapses; bottom, sustained remissions. Each patient is represented by a horizontal bar. Start of treatment is at 0 months. Estimated duration of thyrotoxicosis before treatment, indicated by clear bar extending to the left of 0, was arbitrarily limited to 12 months. This portion was omitted if pretreatment duration was uncertain. Shaded portion indicates duration of antithyroid treatment; termination of solid portion shows that the patient had become euthyroid, and termination of stippled portion indicates end of treatment. Clear portion of each bar to the right indicates how long the patient remained euthyroid after stopping therapy for the relapse group (top) or how long the patients had been followed up for the remission group (bottom).⁹

Serious complications from antithyroid drugs are quite rare, agranulocytosis being the most dangerous. Routine weekly blood cell counts are of little prophylactic value, since agranulocytosis can develop in a patient with a normal leukocyte count within a few hours. It is best to warn the patient that symptoms of fever, malaise, or sore throat are potentially serious and that a physician should be contacted immediately when such problems occur. Fortunately, with current methods of combating infection, agranulocytosis is rarely fatal. There is usually a spontaneous recovery of leukocyte production within one to two weeks

after stopping treatment with the drug. Radioactive iodine therapy is employed once the patient no longer has acute bone marrow depression.

Minor drug toxicity, such as skin rash or severe itching, occurs in 3% to 5% of patients treated with thionamide drugs. It may subside spontaneously if the drug use is continued, or it may disappear if the other drug is substituted, (eg, from propylthiouracil to methimazole). In our clinic, if the problem continues, we stop antithyroid therapy and treat the patient with radioactive iodine.

Special Therapeutic Problems

Pregnancy: I believe that antithyroid drugs are the treatment of choice in thyrotoxic pregnant women. Radioactive iodine is obviously contraindicated because of the danger of fetal thyroid damage. Surgery carries a greater risk than antithyroid drug therapy. Although antithyroid drugs are transported across the placenta to the fetus whereas thyroid hormone is not, if the dose of antithyroid drugs is kept to the minimum necessary to keep the patient from having more than mild hyperthyroidism during the last trimester (usually half the normal dose, ie, 15 mg of methimazole or 150 mg of propylthiouracil daily), the risk of fetal goiter or hypothyroidism is negligible. In treating more than 200 pregnant thyrotoxic patients in our clinic, we have never seen hypothyroidism in a newborn, and only in one instance was there a slight neonatal goiter, which rapidly regressed.

If antithyroid drug therapy is continued postpartum, the mother should not nurse the baby since antithyroid drugs are also transmitted in the milk. Neonatal thyrotoxicosis is an extremely rare malady in the babies of mothers with either active or inactive Graves' disease. This possibility should be borne in mind in checking the infant postnatally. Neonatal thyrotoxicosis usually subsides spontaneously within a few weeks or months and may not require specific therapy.

Thyrotoxicosis in Children: The management of thyrotoxicosis in children is no different than in adults. Children seem to require a proportionately larger dose of antithyroid medication for their size than do adults. Therefore, we usually employ the same daily dose (eg, 30 mg of methimazole) as in adults. Using once-a-day antithyroid therapy is especially important in obtaining patient compliance in children because of the difficulty in keeping them on an eight-hour regimen.

Thyroid Storm (Incipient or Actual): Although full-blown thyroid storm is rare, severe thyrotoxicosis with the potential danger of storm is not. Thyroid storm is a life-threatening problem in which there is hyperpyrexia, delirium, and extreme agitation. Many procedures recommended for this condition, such as huge doses of thionamide drugs, intravenous iodide administration, etc, are of little practical or theoretical value since it takes days or

weeks for them to have any significant effect. Current evidence indicates that the primary cause of thyroid storm may be a marked increase in β -adrenergic effect rather than an acute increase in thyroid hormone concentration.¹⁰ The β -blocker, propranolol, is extremely effective in treating thyroid storm, but it may have to be given in large doses, 20 to 80 mg every four hours orally. A dose of 1 to 3 mg intravenously every four hours may be required in patients unable to take oral medication. Ancillary measures include cooling and sedation.

In the more common situation of incipient thyroid storm, propranolol in a dose of 20 to 40 mg every six to eight hours is usually adequate to control the tachycardia, nervousness, and tremor while treatment of the underlying thyroid problem with antithyroid drugs is being accomplished. In exceptional patients, up to several hundred milligrams per day of propranolol may be necessary.

To prescribe any drug mentioned in this article, the readers should consult full prescribing information.

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