Treatment of Graves' Hyperthyroidism: Evidence-Based and Emerging Modalities

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KEYWORDS

• Graves' disease • Hyperthyroidism • Goiter
• Antithyroid drugs • Radioactive iodine • Thyroidectomy

The etiology of Graves' disease (GD) presently is thought to be based on genetic susceptibility interacting with a number of known and unknown environmental or intrinsic factors.[1,2] Therefore, its treatment optimally would be based on modifying these environmental triggers, of which smoking is best documented.[3,4] Without the potential breakthrough of a novel, biologically modifying class of drugs, such as the B-cell–depleting drug rituximab (RTX),[5] knowledge of the effects and side-effects of the available routine therapeutic options has changed only to a limited degree during the past 50 years. Antithyroid drug (ATD) therapy and radioactive iodine (^{131}I; RAI) have been used for more than half a century, and thyroidectomy has been used for more than 100 years. The main advances during the last couple of decades have been the improved knowledge of factors associated with the maximum efficacy of any therapeutic choice, the increased focus on tailoring the therapy to the individual patient, and recognition of the advantages gained by the patient's active participation in the decision-making process. Consequently, congruent phenotypic presentations may not always lead to the same choice of therapy. Besides physician and patient preferences, factors such as the availability of surgical expertise and restrictions in outpatient RAI use may be decisive.

This article discusses the efficacy, side-effects, cost, and influence on quality of life of all the therapeutic options, insofar as data are available. The focus is on the short- and long-term influence of the therapy on thyroid function and size. Special situations such as therapy during pregnancy and during lactation, in childhood and adolescence, in the elderly, and in case of thyroid storm are discussed in passing. A discussion of

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the treatment of extrathyroidal manifestations of GD, such as Graves' ophthalmopathy or dermopathy (pretibial myxedema), is beyond the scope of this article.

ANTITHYROID DRUGS

Clinical Pharmacology

ATDs, known as thionamides, were introduced into clinical practice in the early 1940s. Propylthiouracil (PTU) and methimazole (MMI) are the preferred drugs in the United States, Europe, and Asia; carbimazole, a prodrug of MMI, is the preferred drug in the United Kingdom. Their major action, after active concentration by the thyroid, is to inhibit thyroid hormone synthesis by interfering with thyroid peroxidase (TPOAb)–mediated iodination of tyrosine residues in thyroglobulin.[6] Other effects relate to the blocking of the conversion of thyroxine (T4) to triiodothyronine (T3), but these effects are seen only with PTU and are of limited clinical importance in most cases. Other effects may rely on immunosuppression, as suggested by a decrease in thyrotropin receptor antibodies (TSHRAb), intracellular adhesion molecule, and soluble interleukin-2 and interleukin-6 receptors, as well as decrease in HLA class II expression. Whether these and other changes are caused by the effect of the drug per se on the immune system or by the simultaneous normalization of thyroid function is still a matter of debate.[6,7]

Both PTU and MMI are absorbed rapidly and nearly completely from the gastrointestinal tract. **Table 1** gives the pertinent properties of the two drugs and the differences between them. Importantly, dose adjustment is not necessary in children, in the elderly, or in persons who have impaired liver or kidney function.[6,8]

Clinical Use of Antithyroid Drugs

ATDs can be used in two ways: either as the primary treatment for hyperthyroidism in an attempt to achieve remission (defined as biochemical euthyroidism for a minimum

Table 1
Comparison of characteristics of the thionamides methimazole and propylthiouracil in the treatment of Graves' disease

Characteristic	Methimazole	Propylthiouracil
Relative potency	10–50	1
Administration	Oral	Oral
Absorption	Nearly complete	Nearly complete
Binding to serum proteins	Negligible	80%–90%
Serum half-life (hours)	4–6	1–2
Volume of distribution (L)	40	20
Duration of action (hours)	> 24	12–24
Metabolism during liver disease	Decreased	Normal
Metabolism during kidney disease	Normal	Normal
Transplacental passage	Low	Even lower
Level in breast milk	Low	Even lower
Inhibition of T4/T3 conversion	No	Yes
Dosing[a]	1–2 times daily	2–3 times daily

[a] At initial therapy. During titrated ATD therapy, when doses of 5 mg methimazole or 100 propylthiouracil are reached, once-daily dosing is considered prudent and probably secures a higher compliance than the use of divided doses.