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Expert Opinion

An update on the pharmacological management of hyperthyroidism due to Graves' disease

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Pharmacological treatment, usually by thionamides (carbimazole, methimazole, propylthiouracil) is, in addition to radioiodine therapy and thyroidectomy, one of the available therapies for Graves' hyperthyroidism. Thionamides represent the treatment of choice in pregnant women, during lactation, in children and adolescents and in preparation for radioiodine therapy or thyroidectomy. Side effects are relatively frequent but are in general mild and transient. Two main regimens are available: titration method (use of the lowest dose maintaining euthyroidism; duration: 12 – 18 months) and block-and-replace method. Neither one has clear advantages in terms of outcome but the latter method is associated with more frequent side effects. Hyperthyroidism relapses in ~ 50% of patients, to whom ablative therapy should be offered.

Keywords: Graves' disease, hyperthyroidism, methimazole, propylthiouracil, thionamides

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1. Introduction

Graves' disease is an autoimmune thyroid disorder characterised, in its classical form, by goitre, hyperthyroidism, ophthalmopathy and, less frequently, dermopathy (pretibial myxedema) [1]. Hyperthyroidism is ultimately due to autoantibodies reacting with the thyroid stimulating hormone receptor (TSH-receptor antibody; TRAb) and causing uncontrolled stimulation of thyroid function and growth [1]. TRAb is found in ~ 80 – 90% of untreated Graves' patients [1]. Graves' disease is the most common form of hyperthyroidism in iodine-sufficient areas, with a prevalence of 2.7% in women and 0.3% in men [1]. The female/male ratio is ~ 6 – 7:1, and the peak age of distribution is in the third to forth decades of life [1].

The ideal treatment of Graves' hyperthyroidism would consist of the elimination of disease triggers, but this is not currently feasible. Therefore, treatments are aimed either at destroying the damaged thyroid (thyroidectomy, radioiodine therapy) or at controlling hyperthyroidism while waiting for a possible remission. Although the mechanisms of remission are not fully understood, it may result from a change in the nature of TRAb; from a stimulating to a blocking antibody [2]. In addition, all immunological features may fade away, including thyroid autoantibodies, TRAb and evidence of T lymphocyte sensitisation [3]. The latter phenomenon may occur in Graves' patients with less severe immunoregulatory defects [2].

Pharmacological treatment of Graves' hyperthyroidism is carried out by the use of thionamides; antithyroid drugs which inihibit thyroid hormone synthesis. Thus, although thyroidectomy and radioiodine are thyroid ablative therapies leading to hypothyroidism, antithyroid drug treatment is a conservative therapy leaving the thyroid gland able to produce thyroid hormones.

Table 1. Selection of different treatment modalities for hyperthyroidism due to Graves' disease.

	Thionamides	Radioiodine	Thyroidectomy
First episode of hyperthyroidism			
Young age	Yes	No*	Yes‡
Adult	Yes	Yes	Yes§
Relapse of hyperthyroidism			
Young age	Yes¶	No*	Yes‡
Adults	No	Yes	Yes§
Pregnancy	Yes	No	Yes#
Lactation	Yes	No	Yes
Suspected malignancy	No	No	Yes
Elderly	No**	Yes	Yes‡‡
Ophthalmopathy	Yes	Yes§§	Yes
Side effects	Yes¶¶	Yes##	Yes***

*Radioiodine has been used in children and adolescents, apparently with no long-term complications; the authors prefer to use it after completion of linear growth and sexual development. ‡If goitre is particularly large in the presence of complications from, or poor compliance with, thionamides. §If goitre is large and the patient refuses radioiodine, there is intolerance to thionamides or suspicion of associated malignancy. ¶As an alternative to thyroidectomy. #It is seldom necessary to be performed in the second trimester. **Usually in preparation for definitive therapy only. ‡‡Radioiodine is preferable if the patient's general condition represents a high surgical risk. §§Radioiodine administration must be associated with concomitant glucocorticoid treatment. ¶¶Although relatively frequent, they are, in general, mild and transient. ## Progression of ophthalmopathy is the only risk (see above); hypothyroidism is a desired goal. ***Hypoparathyroidism and laryngeal nerve paralysis are rare if the surgeon is expert; hypothyroidism is a desired goal.

Selection from the different forms of treatment depends on a series of factors, as illustrated in **Table 1**. Preconditions for antithyroid drug treatment include young age (children and adolescents), small goitre, first episode of hyperthyroidism, pregnancy, lactation, refusal of surgery or radioiodine therapy [1]. Radioiodine therapy is required when hyperthyroidism relapses following antithyroid drug treatment, in the presence of a small goitre (although larger goitres can be successfully treated by radioiodine), when the patient is > 18 years of age, in the elderly and when surgery is not accepted [1]. Whether or not radioiodine therapy represents the treatment of choice in patients with Graves' ophthalmopathy remains a matter of contension. Radioiodine can cause the progression of pre-existing ophthalmopathy (particularly in smokers) in ~ 15% of cases but this untoward effect can easily be prevented by a concomitant short course of moderate doses of glucocorticoids [4]. Other factors, such as smoking, late correction of postradioiodine hypothyroidism and pre-existing active ophthalmopathy, are likely to contribute to this adverse effect of radioiodine [4]. This modality of treatment is contraindicated in pregnancy and during lactation. Radioiodine therapy is considered by many physicians, particularly in US, to be the treatment of choice in the first episode of hyperthyroidism. Hypothyroidism following both radioiodine administration or thyroidectomy should not be considered an undue effect but a desired goal. Surgery (total or near-total thyroidectomy) is required after the recurrence of hyperthyroidism following antithyroid drug treatment in patients < 18 years of age, when the goitre is large (particularly if signs and/or symptoms of tracheal or oesophageal compression are present), if the patient does not want to be treated by radioiodine therapy or if there is suspicion of associated malignancy in a nodular lesion [1]. Hypothyroidism is inevitable. The course of the ophthalmopathy is not affected by thyroid surgery. Complications, such as hypoparathyroidism and laryngeal nerve damage, are infrequent (1 – 2%) if the surgeon is expert.

2. Antithyroid drug treatment

2.1 Thionamides

The main drugs used in the management of Graves' hyperthyroidism are thionamides. These include carbimazole, its active metabolite, methimazole (MMI), and propylthiouracil (PTU). Carbimazole, mainly used in the UK, is rapidly converted to MMI and can be considered equivalent to it. MMI is the most commonly used thionamide in Europe and Japan, whereas PTU is the most prescribed antithyroid drug in the US and South America.

MMI and PTU are the antithyroid drugs of common use for the management of hyperthyroidism due to Graves' disease. Both drugs are given orally and almost completely absorbed from the gastrointestinal tract. Although MMI binding to serum proteins is negligible, PTU is largely (75 – 80%) bound, mainly to albumin [5] (**Table 2**). The serum half-life of MMI is longer than that of PTU (5 – 6 versus 1 – 2 h); the duration of MMI action is also longer (> 24 versus 12 – 24 h for PTU), likely owing to its slower intrathyroidal turnover [5] (**Table 2**).

Table 2. Pharmacological characteristics of thionamides.

	Methimazole	Propylthiouracil
Relative therapeutic potency	10 – 50	1
Absorption	Almost complete	Almost complete
Binding to serum proteins	Negligible	75 – 80%
Half-life in serum (h)	5 – 6	1 – 2
Duration of action (h)	> 24	12 – 24
Transplacental transfer	Low	Maybe lower
Passage into milk	Low	Lower
Route of administration	Oral	Oral
Administration schedule	Once daily	2 – 3 times daily
Thyrotoxic storm		Intravenous PTU available in some countries

PTU: Propylthiouracil.

This has important implications because MMI can usually be given as a single daily dose, whereas PTU, at least in the initial phases of treatment, must be administered in 2 – 3 daily doses. Both drugs cross the placenta and can be found in the milk but this phenomenon is limited, particularly with PTU in view of its very low lipid solubility [5]. The therapeutic potency of MMI is more than 10-fold greater than that of PTU [5] hence, doses of MMI required to control hyperthyroidism are lower than those of PTU. This factor may show MMI to be superior; however, the choice between the two thionamides is largely related to personal preference and/or local availability. Cost may also be an issue because in the US in 1999 the cost of 100 tablets was ~ $20 for PTU and $80 for MMI [6]; conversely, in the UK PTU is more expensive than carbimazole.

2.2 Non-thionamide drugs

Drugs other than thionamides have a limited role or are used only under special circumstances [1,5]. Lithium carbonate is a weak antithyroid drug but can be used before and after radioiodine therapy to avoid radioiodine-associated (and MMI withdrawal-associated) rise in serum thyroid hormone levels [7] (see Section 2.8.5). Stable iodine is utilised in the preparation to thyroidectomy (see Section 2.8.6) because, besides its effect on thyroid hormone release from the thyroid, it decreases thyroid blood flow and may, therefore, reduce perioperative blood loss [1,5]. Iodine is also employed in thyrotoxic storm (see Section 2.8.8). Oral iodinated contrastographic agents, such as iopanoic acid and sodium ipodate, reduce thyroid hormone release and peripheral conversion of thyroxine (T4) to triiodothyronine (T3), and can be used, in combination with thionamides, when severely thyrotoxic patients must urgently be submitted to thyroidectomy [8,9], in neonatal hyperthyroidism [10] (see Section 2.8.3) and in thyrotoxic storm (see Section 2.8.8). However, escape from inhibition occurs, as with stable iodine, within a few weeks, therefore, these agents cannot be employed either as the sole therapy for hyperthyroidism or on a long-term basis [11]. Potassium perchlorate is mainly used in association with thionamides when Graves' hyperthyroidism is complicated by iodine load, as with amiodarone-treated patients [12] (see Section 2.8.7). Because of its potential toxicity, it should be used neither for > 4 – 6 weeks nor at daily doses > 1 g [12]. Its main action is to deplete intrathyroidal iodine stores, thus rendering thionamides more effective. β-Adrenergic antagonists are useful to control symptoms and signs of hyperthyroidism, such as tachycardia and tremors in the first phases of treatment, when the patients is thyrotoxic, and shortly after radioiodine therapy, when hyperthyroidism is unlikely to be fully controlled. Glucocorticoids are not indicated in the management of Graves' hyperthyroidism, despite the autoimmune nature of this disease but they do have a role in the management of thyrotoxic storm [1] (see Section 2.8.8).

2.3 Mechanism of action of thionamides

Thionamide neither inhibits active thyroidal iodide transport into the thyroid nor blocks the release of stored hormones from the thyroid. Accordingly, control of hyperthyroidism is not immediate and can require weeks, depending on the severity of hyperthyroidism and intrathyroidal hormone stores. The effectiveness of thionamides is reduced if intrathyroidal iodine content is high (see Section 2.8.7). The main action of intrathyroidal thionamide is to inhibit thyroid hormone synthesis [1]. This is accomplished because thionamides act as a preferential substrate for thyroid peroxidase, the enzyme that catalyses iodide oxidation, the iodination of tyrosine residues onto thyroglobulin and the coupling of iodotyrosines (monoiodotyrosine and diiodotyrosine) to form T4 and T3. In this way, thionamides compete with thyroglobulin-linked tyrosine residues and divert oxidised iodide from hormone synthesis [13] (**Table 3**). PTU but not MMI, inhibits type I 5′-deiodinase activity, thus leading to a decrease in peripheral T4 deiodination and T3 formation [1] (**Table 3**). Evidence derived from *in vitro* studies suggests that thionamides may have immunomodulatory actions, which

Table 3. Mechanism of action of thionamides.

Action	Effect
Inhibition of iodide uptake	No
Inhibition of tyrosine residue iodination	Yes*
Inhibition of iodotyrosine coupling	Yes*
Inhibition of thyroid hormone release	No
Inhibition of type I 5¢-deiodinase	Yes‡

*These actions are mediated by the inhibition of thyroid peroxidase. ‡Only for propylthiouracil.

may represent part of their therapeutic effect in autoimmune Graves' disease [14]. However, it seems that these effects on immune reactions *in vitro* can only be observed using doses higher than those achieved *in vivo* during antithyroid drug treatment. Changes in autoimmune phenomena *in vivo* (e.g., decrease in serum TRAb levels or changes in T-cell subsets) may simply reflect the correction of thyroid hyperfunction, which *per se* may theoretically contribute to the maintainence of the thyroid autoimmune phenomena through persistent antigen exposure.

2.4 Side effects of thionamides

Thionamide treatment can be considered a safe treatment. Overall, adverse effects of thionamides, although relatively common (~ 10% of patients), are usually mild and self-limiting, whereas serious side effects occur in < 5% of cases [15] (**Table 4**). They are more common during the initial phases of treatment, when drug dosage is higher. If an adverse effect is observed with one drug, the other thionamide can be substituted but crossreactivity is a frequent phenomemon (~ 50%) [15]. Minor effects include skin rash with urticaria and itching, arthralgia and mild gastrointestinal disturbances. Although relatively common, these phenomena are transient, tend to subside spontaneously or with antihistamines (in the case of of skin rash) and usually do not require drug withdrawal. Transient and mild leukopenia can be observed in 10% of adults and ≤ 25% of children. Agranulocytosis (neutrophil count < 0.5×10^9/l) is one of the most serious complications of treatment [15]; it occurs in 0.1 – 0.5% of patients, develops abruptly and requires immediate thionamide withdrawal and prompt treatment with antibacterials. The administration of granulocyte colony-stimulating factor (G-CSF) may reduce the time required to restore normal granulocyte count and the time of hospitalisation [16], but a randomised and controlled trial failed to demonstrate any difference in the recovery time between untreated patients and patients given G-CSF [17]. Although there seems to be a dose-dependency of this serious complication in the case of MMI, it is lacking in the case of PTU [15]. The abrupt and explosive onset of agranulocytosis makes routine leukocyte counts fruitless, however, patients should be advised that in case of fever, sore throat or other signs of infections, a leukocyte count should be obtained

Table 4. Side effects of thionamides.

	Adverse effect	Frequency
Blood	Mild leukopenia	Relatively frequent
	Agranulocytosis	Rare (0.1 – 0.5%)
	Aplastic anaemia	Very rare
	Thrombocytopenia	Very rare
Skin	Skin rash	Relatively frequent
	Urticaria	Relatively frequent
	Itching	Relatively frequent
	Aplasia cutis	Very rare (MMI)
Liver	Hepatocellular necrosis	Very rare (PTU)
	Cholestasis	Very rare (MMI)
Collagen	Arthralgias	Uncommon
	SLE-like syndrome	Very rare (PTU > MMI)
	Vasculitis	Very rare (PTU > MMI)
Miscellaneous	Loss of taste	Rare (MMI)
	Hypothrombinaemia	Rare (PTU)
	Insulin autoantibodies	Very rare

MMI: Methimazole; PTU: Propylthiouracil; SLE: Systemic lupus erythematosus.

rare but serious side effects (**Table 4**) include; aplastic anaemia, hepatocellular necrosis (PTU), cholestasis (MMI), systemic lupus erythematosus-like syndrome, antineutrophil cytoplasmic antibody-related vasculitis, hypothrombinaemia (PTU), hypoglycemia due to insulin autoantibodies and loss of taste (MMI) [15]. Aplasia cutis (i.e., the congenital absence of skin; localised or disseminated, most commonly limited to the scalp) has been reported in a few infants born to hyperthyroid mothers given MMI during pregnancy, whereas no such cases have been reported in those following PTU treatment [18]. Very rare cases of embriopathy (choanal and oesophageal atresia, cardiac defects) have been reported in infants born to mothers given high doses of MMI early in pregnancy [19] (see Section 2.8.1).

2.5 Different dose regimens

Two different regimens of thionamide therapy are commonly in use. The titration method is aimed at using the lowest thionamide dose mainitaining euthyroidism; the second regimen, the block-and-replace method, employs persistently high doses of thionamides in association with L-T4 replacement to avoid hypothyroidism (**Table 5**).

In the titration method, the usual starting dose of thionamides is MMI 20 – 30 mg/day, either in a single dose or in divided doses, or PTU 300 – 400 mg, always in divided doses. The initial dose depends, at least in part, on the severity of hyperthyroidism; a lower dose of thionamide in patients with severe hyperthyroidism may be inadequate to rapidly control thyroid hyperfunction, a higher dose in patients with mild

Table 5. Features of titration method and block-and-replace method.

Method	Features
Titration method	Initial moderate-to-high doses of thionamides. Dosage is then tapered down to the lowest daily dose maintaining euthyroidism. No l-T4 is added. Duration of treatment: 12 – 18 months.
Block-and-replace method	High doses of thionamides are given for the whole period. l-T4 is added in order to avoid hypothyroidism. Duration of treatment: 6 months.

hyperthyroidism may lead to hypothyroidism [20]. Further to periodic assessment of thyroid function by serum-free thyroid hormone measurement (serum TSH remains suppressed for several weeks to a few months after the restoration of euthyroidism), daily dosage of the drug is tapered down (unless the block-and-replace regimen is selected) to the lowest effective dose. It is not unusual that a daily dose of MMI 2.5 – 5 mg or PTU 50 – 100 mg is sufficient for good metabolic control. Euthyroidism is usually achieved within 4 – 12 weeks. Assessment of thyroid status should be made every 4 – 6 weeks for the first 4 – 6 months, and then evey 3 – 4 months until the end of treatment, usually after 18 – 24 months.

In the block-and-replace method, deliberately high doses of thionamides are given together with L-T4 [21]. This regimen has advantages and disadvantages over the titration method. Higher doses may theoretically exert an immunosuppressive effect useful to achieve permanent remission of the disease. However, this putative effect remains to be demonstrated. With the block-and-replace regimen, avoidance of hypothyroidism seems to be simpler than with the titration method, and because the maximal effect is achieved after 6 months, treatment is shorter and the number of visits lower. On the other hand, the prolonged use of higher doses of thionamides (e.g., MMI 30 – 40 mg/day) exposes the patient to a higher risk of side effects and complications. In addition, the high number of tablets that the patient must take every day may create problems of poor compliance. Finally, cost of this combined treatment is higher, at least in the 6-month period.

A recent systematic review of randomised or quasi-randomized studies showed that that the block-and-replace regimen does not offer any advantages in terms of permanent remission of hyperthyroidism, although it bears a higher risk of side effects [22]. Accordingly, the authors favour the use of the titration method as the therapeutic regimen of choice for antithyroid drug therapy but others may equally prefer the block-and-replace method.

A third therapeutic regimen of antithyroid drug therapy was proposed several years ago in Japan [23]. After restoring euthyroidism with MMI alone, patients were randomised to continue for 12 months with either MMI alone or MMI and L-T4; the latter group then continued treatment with L-T4 for additional an 36 months. Relapses in the L-T4-treated group were significantly lower than in the group not receiving L-T4 (2 versus 35%) [23]. Unfortunately, this study has not been reproduced by several studies thereafter, in which either L-T4 or L-T3 were used after thionamide withdrawal [24-30]. One study indeed showed that L-T4 administration after antithyroid drug therapy was associated with increased recurrence of hyperthyroidism [31]. The reason for this discrepancy remains unclear but the number of negative studies suggests that the addition of L-T4, as originally proposed by the Japanese group [23], is not useful.

2.6 Duration of treatment

Early studies suggested that short-term thionamide treatments (3 – 4 months) were as (poorly) effective as long-term treatments (12 – 18 months). However, using the titration method, more recent studies have documented that an 18-month treament with carbimazole was associated with a significantly lower relapse rate than a 6-month treatment [32]. On the other hand, extension of thionamide therapy up to 24 or 42 months does not increase the rate of positive outcome of antithyroid drug treatment [33], although the use of high doses of thionamides may result in a longer relapse-free period following thionamide withdrawal [34]. Using the block-and-replace regimen, prolongation of treatment from 6 months to 12 months does not increase the chance of achieving permanent remission of hyperthyroidism [35].

Thus, using the titration method, the best duration of treatment is 12 or, better yet, 18 months whereas, with the block-and-replace method, treatment should not be continued beyond 6 months.

2.7 Results of treatment

The major drawback of thionamide antithyroid drug treatment is the high rate of treatment failure. Although, as previously discussed, the latter can be influenced by the duration of treatment (but not by the use of high doses of thionamides), at the end of the programme ~ 30 – 70% of patients experience a relapse of hyperthyroidism [36]. This may occur at any time after thionamide withdrawal but most recurrences are observed within the first year after discontinuation of treatment [36]. However, it should be noted that hyperthyroidism may recur even years after thionamide withdrawal [34]. This observation, in additon to the notion that in the long run ~ 15% of thionamide-treated patients become hypothyroid, underscores the need for a lifelong follow-up of Graves' patients after the completion of antithyroid drug treatment.

There are no reliable predictors of the outcome of thionamide treatment. However, as illustrated in **Table 6**, patients with large goitres that do not shrink during treatment, those with severe hyperthyroidism, which is difficult to control even with

Table 6. Factors affecting the outcome of thionamide antithyroid therapy.

Variable	Relapse rate is higher if:
Goitre size	Goitre is large
Age	Patient is young
Gender	Patient is a man
Metabolic control during treatment	Hyperthyroidism is difficult to control and requires high doses of thionamides
Smoking	Patient smokes
TRAb	TRAb is present at the end of thionamide treatment*

*Relapses are also frequent in patients whose TRAb tests are negative at the end of thionamide treatment.
TRAb: TSH-receptor antibody.

relatively high doses of thionamides (MMI 20 – 30 mg/day or equivalent), and those showing TRAb levels that do not decrease during treatment, are indeed very good candidates to have a relapse of hyperthyroidism [36]. Patients having the above characteristics may be candidates for longer thionamide treatments, but whether the long-term outcome is improved in such a way is uncertain. Failure of TRAb to become undetectable almost invariably leads to a relapse of hyperthyroidism following thionamide withdrawal but, also, patients whose TRAb levels become undetectable during treatment have a relatively high chance of experiencing a relapse of Graves' hyperthyroidism [36]. The use of newly developed TRAb assays, using recombinant human TSH characterised by higher sensitivity and specificity [37], may help improve the diagnostic and predictive capacity of TRAb assays in the management of Graves' hyperthyroidism.

Men have a lower remission than women [38], whereas young age (< 40 years) seems to be associated with a higher relapse rate [38], possibly because hyperthyroidism tends to be less severe in the elderly. Smoking has been reported to reduce the likelihood of achieving a stable remission of hyperthyroidism [28,39].

Although in children and adolescents a second course of antithyroid drug treatment is required if hyperthyroidism relapses, in adults, recurrence of hyperthyroidism after thionamide therapy is an indication to switch to ablative therapy by either radioiodine or thyroidectomy, because the chance of attaining stable remission of hyperthyroidism with a second course of thionamides is low. A possible exception to this rule may be represented by the rare event of a second episode of Graves' hyperthyroidism occurring many years after the completion of a course of thionamide treatment.

2.8 Special situations

2.8.1 Pregnancy and lactation

Untreated hyperthyroidism in pregnancy bears the risk of low birth weight, prematurity, stillbirth, a small increase in congenital malformations and pre-eclampsia [18]. Thus, control of thyroid hyperfunction is mandatory, although autoimmune hyperthyroidism due to Graves' disease generally tends to spontaneously improve during pregnancy, mainly because this condition is naturally associated with partial immunosuppression [18]. Conversely, Graves' hyperthyroidism, like chronic autoimmune (Hashimoto's) thyroiditis, may develop or be exacerbated in the postpartum period [18]. Thionamides represent the treatment of choice for Graves' pregnant women because radioiodine therapy is contraindicated in pregnancy (as well as during lactation), and surgery is only exceptionally required [18]. Both MMI and PTU have been used during pregnancy, although PTU has long been preferred in the US because of its purported lower transplacental trasnfer due to its low lipid solubility and higher transport protein binding. However, the concept that transplacental passage of PTU is lower than that of MMI has recently been challenged [40]. As mentioned in Section 2.4, rare cases of aplasia cutis and embriopathy have been reported in the offspring of mothers given MMI but not PTU [18]. It should, however, be mentioned that embriopathy was associated with exposure to high doses of MMI during early pregnancy [19]. The above considerations seem to highlight PTU as the preferred choice, at least during the first trimester of pregnancy when organogenesis takes place, particularly if high doses of thionamides are needed to control hyperthyroidism. The goal of antithyroid drug treatment during pregnancy is to use the lowest dose of thionamides that is sufficient to maintain free thyroid hormones in the high-to-normal range, avoiding the risk of fetal hypothyroidism and goiter on one hand, and the risk that even mild maternal hypothyroidism may affect subsequent neuropsychological development in the offspring on the other [18].

The use of thionamides during lactation appears to be safe, and doses of MMI 20 mg/day do not affect the newborn's thyroid function [18]. PTU is also safe for breastfeeding. In view of thionamide pharmacokinetics, it seems wise to suggest that the thionamide pill be taken shortly after breastfeeding.

2.8.2 Children and adolescents

Thionamide treatment represents the first-line treatment for the majority of children and adolescents affected with Graves' disease [41]. Radioiodine therapy or thyroidectomy

Table 7. Thionamide treatment and outcome of radioiodine therapy.

Thionamide treatment	Efficacy of radioiodine therapy
Prior to radioiodine administration	Reduced with propylthiouracil, not with methimazole
Concomitantly to radioiodine	Reduced
Shortly after radioiodine	Reduced

are valid alternatives if thionamides do not effectively control hyperthyroidism (especially if goitre is large) or compliance with therapy is poor. Sometimes it is necessary to switch to ablative treatments because of drug side effects, which are more common in young patients. Treatment is usually longer than in adults and may last for several years. Longer duration of treatment has been associated with higher cure rates [41]. One study showed that > 75% of children and adolescents treated with thionamides for > 11 years remained in remission [42]. Every effort is usually made to continue thionamide therapy until completion of physical growth and sexual development; treatment is then interrupted and, in the case of relapse, switched to ablative therapy by either radioiodine or thyroidectomy.

2.8.3 Neonatal hyperthyroidism

This is due to transplacental passage of TRAb from the maternal side [43]. Because of this pathogenic mechanism, it is a transient condition; nevertheless, a vigorous treatment with thionamides, in association with propranolol or other β-adrenergic antagonists and iodine (or oral iodinated contrastographic agents [44]) is warranted.

2.8.4 Ophthalmopathy

Radioiodine therapy can cause the progression of Graves' ophthalmopathy in ~ 15% of cases [2], particularly in patients who have pre-existing ophthalmopathy and are smokers [2], or whose postradioiodine hypothyroidism is not promptly corrected by L-T4 replacement therapy; on the contrary, neither thyroidectomy nor antithyroid drug treatment substantially influence the course of eye disease [45]. However, the correction of hyperthyroidism using thionamide therapy may be accompanied by an improvement of ocular involvement [46]. An open issue is whether hyperthyroidism of patients who have associated Graves' ophthalmopathy should be treated by conservative therapy (thionamides) or ablative therapy (radioiodine therapy or thyroidectomy) [47]. Because Graves' ophthalmopathy is probably initiated by autoimmune reactions directed against antigen(s) shared by the thyroid and the eye, many experts believe that complete removal of thyroid antigens (and intrathyroidal autoreactive T lymphocytes) may be associated with an amelioration of the ophthalmopathy [48]. Others suggest that this approach would not affect the course of eye disease once it has been triggered. No final answer is available to this problem but the authors favour ablative therapy rather than thionamide therapy in patients with substantial ocular involvement.

2.8.5 Thionamide treatment before, during and after radioiodine therapy

Whether the pretreatment of Graves' hyperthyroidism with thionamides affects, namely reduces, the effectiveness of subsequent radioiodine therapy is a matter of long debate, based mainly on retrospective studies. Two recent prospective, randomised studies demonstrated that pretreatment with MMI does not reduce the cure rate of hyperthyroidism after radioiodine therapy [49,50]. On the other hand, a recent randomised clinical trial showed that pretreatment with PTU was associated with associated with a reduced cure rate [51]. Thus, it would seem that, in agreement with previous reports, only PTU pretreatment may lower the efficacy of radioiodine, probaly owing to the fact that its radioprotective effect lasts longer than that of MMI (**Table 7**). This problem can, however, be overcome by increasing the administered dose of radioiodine by 25% [52]. Pretreatment with thionamides has the clear beneficial effect of controlling hyperthyroidism; this is mandatory in the elderly and in patients with relevant comorbidity [53]. Leaving the patient untreated prior to radioiodine administration exposes him/her to a prolonged period of uncontrolled hyperthyroidism, as radioiodine takes several weeks to be fully effective. Another positive aspect of preradioiodine thionamide treatment is that it depletes intrathyroidal iodine stores, thus limiting a possible rise in serum thyroid hormone levels after radioiodine-induced thyroid damage [54]. In this regard, it is worth mentioning that after thionamide withdrawal, 4 – 5 days prior to radioiodine therapy, a short course of lithium carbonate, to be continued for 2 weeks after radioiodine administration, effectively prevents any increase in serum thyroid hormone levels either due to thionamide withdrawal to radioiodine cytotoxicity [7], and is associated with a more prompt control of hyperthyroidism and goiter shrinkage after radioiodine [55]. If thionamide pretreatment (at least using MMI) does not seem to reduce radioiodine effectiveness, available data convincingly indicates that the continuation of antithyroid drug treatment during radioiodine therapy [56], or its resumption shortly after [57], is associated with a higher rate of treatment failure (**Table 7**). Thus, thionamide treatment should be reinstituted only in at-risk patients (old patients with associated comorbidity) and ≥ 7 – 10 days after radioiodine administration.

2.8.6 *Treatment with thionamides in the preparation to surgery*

Hyperthyroidism must be controlled pharmacologically before thyroidectomy. Thionamides should be given until euthyroidism is restored, and iodide (Lugol's solution or saturated solution of potassium iodide) for 1 – 2 weeks prior to surgery. If surgery is urgent, a combination of oral iodinated contrastographic agents, particularly iopanoic acid, β-adrenergic antagonists and glucocorticoids, should be used because of the delayed effect of thionamides [9].

2.8.7 *Graves' disease occurring in amiodarone-treated patients*

Amiodarone, an iodine-rich antiarrhythmic drug, causes thyroid dysfunction (either thyrotoxicosis or hypothyroidism) in ~ 15% of treated patients [12]. Amiodarone-induced thyrotoxicosis (AIT) can be distinguished into two main forms: type II AIT, a destructive thyroiditis, which must be treated by steroids [12]; and type I AIT. The latter develops in an abnormal thyroid gland, with nodular goitre or latent Graves' disease [12]. Under these conditions, the huge iodine load due to amiodarone administration makes thionamide therapy less effective, owing to high intrathyroidal iodine content [12]. Thus, in type I AIT occurring in a thyroid gland affected with Graves' disease, the addition of potassium perchlorate (see Section 2.2) is useful because this drug depletes intrathyroidal iodine stores and favours the antithyroid effect of thionamides. Potassium perchlorate is usually used for 3 – 6 weeks at doses ≤ than 1 g/day because of its possible toxicity on bone marrow and the kidney [12]. After the correction of Graves' hyperthyroidism complicated by iodine contamination (following amiodarone withdrawal), a definitive therapy by either thyroidectomy or radioiodine (if thyroidal radioactive iodine uptake is high enough) is usually offered, particularly if amiodarone therapy needs to be reinstated for the underlying cardiac problems [12].

2.8.8 *Thyrotoxic storm*

Thyrotoxic storm is a rare form of life-threatening severe hyperthyroidism [58]. It is an endocrine emergency and treatment must be aggressive. It is far less common than in the past, owing to earlier diagnosis and better management of Graves' hyperthyroidism. Thionamides play a major role in its management by reducing thyroid hormone synthesis. Higher than usual doses are employed, such as MMI 20 mg every 4 – 6 h. PTU is preferred by some thyroidologists due to its inhibitory effect on peripheral conversion of T4 to the metabolic active hormone, T3. Inorganic iodide (Lugol's solution, saturated solution of potassium iodide) is an important adjuvant because it inhibits thyroid hormone release from the thyroid; however, it must be initiated after antithyroid drugs because it is necessary that iodide organification be inhibited by thionamides [58]. As an alternative to inorganic iodide, oral iodinated contrastographic agents (iopanoic acid, sodium ipodate) can be utilised [58]. The administration of propranolol or other β-adrenergic antagonists is important to counterbalance peripheral actions of thyroid hormones through the inhibition of type I 5′-deiodinase activity [58]. Plasmapheresis, aimed at removing thyroid hormone from the circulation, should be used only in exceptional cases. General support measures, including volume repletion, external cooling, cardioactive drugs and antibiotics, as appropriate, should also be taken.

3. Expert opinion

Pharmacological treatment for hyperthyroidism due to Graves' disease has been used for > 60 years. There is no doubt that thionamides represent a valid, safe and non-invasive tool to control thyroid hyperfunction. Likewise, it is equally clear that this treatment leads to permanent remission (cure) of Graves' hyperthyroidism only in ~ 50% of treated patients. Search for effective predictors of treatment failure has so far not identified patients who are inevitably destined to relapse and, therefore, may avoid a useless treatment and should be switched to definitive (although destructive) treatments, such as radioiodine or thyroidectomy. Available data indicates that the use of high doses of thionamides does not add any clear advantage compared with the use of the lowest dose of the drug capable to maintain euthyroidism. The addition of L-T4 after thionamide withdrawal does not seem to reduce failure rate. Likewise, although the titration method duration of treatment of 12 – 18 months is associated with a better outcome compared with short-term regimens, the extension of treatment beyond 18 – 24 months does not offer any further advantage in terms of long-term successful outcome. Antithyroid drug therapy is the first-line treatment during pregnancy and breastfeeding, and does not show any link to associated ophthalmopathy. Side effects are limited, especially if low doses are used (but dose-dependency does not seem to exist for PTU).

According to this discussion, our opinion concerning antithyroid drug therapy with thionamides is as follows:

- Thionamides are the first-line treatment in pregnant women, children and adolescents, adults experiencing the first episode of hyperthyroidism and patients who are being submitted to radioiodine therapy or thyroidectomy. This treatment is also indicated in patients with Graves' ophthalmopathy, independently of whether they will be treated with radioiodine or thyrodectomy because control of hyperthyroidism may have some beneficial effects on eye disease.
- We prefer MMI to PTU in view of the lower risk of side effects and the possibility of giving the drug as a single daily dose, thus increasing the patient's compliance. Local availability is also an issue because, for example, PTU is not on the market in Italy. In pregnant women, the risk of MMI-associated aplasia cutis and embriopathy is very low, but the use of PTU, which has never been associated with untoward fetal effects, should be endorsed, at least in the first trimester

of pregnancy. In any case, treatment of pregnant women should employ the lowest dose of thionamides maintaining free thyroid hormone levels in the high-normal range.
- We favour the titration regimen over the block-and-replace regimen because the former is simpler, is likely to be associated with better patient compliance and has a lower incidence of side effects. We do not advise the use of TSH-suppressive L-T4 therapy after MMI withdrawal.
- Duration of treatment should be neither < 12 months nor > 18 months if the titration method is used (or > 6 months with the block-and-replace regimen). An exception to this rule is represented by hyperthyroidism in children and adolescents, who may continue antithyroid drug treatment until somatic growth and sexual development are complete, (i.e., around the age of 18).
- After thionamide withdrawal, follow up should be strict during the first 3 – 12 months because this is the period when most recurrences occur. In case of relapse of hyperthyroidism, we usually do not offer a second course of antithyroid drug treatment but switch to ablative therapy. Because relapse of hyperthyroidism, as well as the onset of hypothyroidism, may occur even later, patients treated with thionamides are bound to lifelong periodical assessment of thyroid status.

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