The Use of Thionamides in Graves' Disease Treatment: A Literature Review

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Abstract

Graves' disease is an autoimmune disorder affecting the thyroid gland with a wide range of clinical manifestations. One of the most notable signs of Graves' disease is hyperthyroidism. In general, there are three options in treating Graves' hyperthyroidism: pharmacological therapy, thyroidectomy, and radioactive iodine therapy. Thionamides, which consist of methimazole, carbimazole, and propylthiouracil, are considered to be the most prominent pharmacological therapy of Graves' disease. Among these drugs, propylthiouracil is the least favored because of its adverse effects.

Keywords: Graves' disease, thionamide, methimazole, carbimazole, propylthiouracil

1. Introduction

Graves' disease is an autoimmune disorder that affects a person's thyroid hormone production. One of the most pathognomonic markers of Graves' disease is the existence of autoantibodies that mimic the actions of thyroid-stimulating hormone (TSH). These autoantibodies can cause the proliferation of thyroid cells, enlargement of the thyroid gland, hence the overproduction of thyroid hormones. The clinical manifestations of this disease range from hyperthyroidism and thyrotoxicosis, to ophthalmopathy, cardiomyopathy, and dermatopathy. [1, 2, 3]

There are many genetic and environmental factors to be considered regarding the production of autoantibodies against thyroid antigens. Some genes (HLA, CD40, CTLA4, PTPN22, and FCRL3) are known to be involved in the pathology of Graves' disease, although they can only explain around 10% of the disease's heritability. Iodine consumption, smoking behavior, stress, bacterial infection, and a number of medications are some of the known environmental factors of Graves' disease. However, the exact stimuli for B cells to produce these autoantibodies remain unknown. Some studies suggested that intrathyroidal CD4+ T helper cells might be responsible for this process. [1, 2, 4]

Since the main cause of Graves' disease is still undiscovered, therapeutic modalities are directed to treat the symptoms, such as thyrotoxicosis and ophthalmopathy [5]. Graves' disease treatment is chosen based on the severity of thyrotoxicosis, age of the patient, size of the struma, availability of treatment, and comorbidities [6]. In treating Graves' disease hyperthyroidism, clinicians usually choose between three kinds of modality: drugs that can decrease the production of thyroid hormones, total thyroidectomy, or radioactive iodine therapy [7].

In Asian, European, and Latin American countries, the thionamides (a class of antithyroid drugs) which are propylthiouracil, methimazole, and carbimazole, are widely used to treat Graves' disease [7]. The goal of this

treatment is to reach euthyroidism, which is a state of normal thyroid functions marked by normal levels of TSH and thyroxine (T4). These medications work mostly by inhibiting thyroid peroxidase, an enzyme involved in the synthesis of thyroid hormones [3].

Thionamides are often the first choice in the treatment of Graves' disease also because there are a lot of situations where these drugs must be preferred over other modalities. They are recommended to be administered to patients with a high chance of remission, patients with contraindication to surgical procedures, or in places where it is just not possible to perform radiotherapy and surgery due to facility limitations [8]. The purpose of this article is to review studies about the use of these drugs in Graves' disease patients.

2. Discussion

2.1. Pharmacology of Thionamides

After being orally administered, propylthiouracil has a relatively good absorption (around 75%). Propylthiouracil then binds to plasma proteins (around 82%) and eventually concentrates in the thyroid gland. This drug begins to have effect after 24 to 36 hours and the duration of action is 12 to 24 hours. In the liver, this drug is extensively metabolized into glucoronides or inorganic sulfates. Propylthiouracil is eventually eliminated through urine excretion (around 35%) as intact and conjugated metabolites. [9, 10]

Methimazole or thiamazole is an active form of carbimazole, so the two drugs have similar pharmacokinetics. Carbimazole itself was initially established to have a longer acting version of methimazole. After being absorbed, carbimazole is rapidly metabolized into methimazole in the serum [11]. It has been discovered that 10 milligrams of carbimazole will be metabolized into 6 milligrams of methimazole [12].

With a bioavailability rate of 93%, methimazole is absorbed extensively following oral administration. This drug does not bind to plasma proteins and has a high concentration in the thyroid gland. In the liver, the drug is largely metabolized and some of its metabolites are known to have antithyroidal mechanisms.Similar to propylthiouracil, methimazole is excreted through the urine. [13]

The initial dose of thionamides is based on the patients' severity of hyperthyroidism, volume of the thyroid gland, and iodine uptake. Carbimazole and methimazole can be taken once a day, while propylthiouracil is usually taken twice to three times per day. Clinicians should be careful when deciding the dose of thionamides. Dosing should be based on each patient's levels of TSH and free thyroxine (FT4). This is to make sure that the thyroid gland will function properly post-treatment and to prevent hypothyroidism as well as other adverse events. [4]

The administration of thionamides should be stopped immediately after a patient reaches euthyroidism. Based on the guidelines, a patient is considered to gain remission if their serum TSH, FT4, and total T3 levels are within normal ranges for up to one year following the withdrawal of treatments. [4]

2.2. Methimazole and Carbimazole as Treatments *of Graves' Disease*

In clinical settings, methimazole and carbimazole are generally preferred over propylthiouracil and used as the first-line treatment of Graves' disease. [14]. A lot of previous studies also reported that these two drugs have a higher remission rate, fewer cases of adverse events, and are considered more compatible with other treatment modalities of Graves' disease.

A retrospective study by Villagelin and colleagues (2015) reported that the daily administration of low-dose methimazole in Graves' disease patients is proven to be safe and effective. This study also compared the success of methimazole and radiotherapy in treating Graves' ophthalmopathy. The results showed that Graves' ophthalmopathy has a higher remission rate when treated with methimazole than radioactive iodine therapy.

Other results of this study also suggested that methimazole is an efficient treatment modality for cases of Graves' recurrency and in Graves' disease patients who reject definitive treatments. [15]

A study from 2019 stated that a long-term methimazole therapy is preferred over a short one. The study followed 302 Graves' disease patients who were not properly treated in their first stages of Graves' disease. All of these patients are then treated with methimazole for 18-24 months, but some of them received longer therapy while the others do not. The results showed that the group with a longer period of methimazole therapy had fewer cases of hyperthyroidism relapse than the group with a more conventional therapy duration [16]. Those results seem to align with a more recent study from 2021 that reported more remissions with longer-term therapy [17].

Higher dose of methimazole has also been proved to have faster response in Graves' disease patients. A study divided Graves' disease patients who were treated with methimazole into two groups: one group were treated with 10 milligrams of methimazole and the other were treated with 40 milligrams of methimazole. The results stated that the latter group showed earlier response than the former group. [18]

Although carbimazole and methimazole are favored in treating Graves' disease, these medications still cause adverse events in some cases. Carbimazole is known to carry a risk of acute pancreatitis [19]. Cutaneous reactions, such as pruritus and hives, are the most common adverse events that can occur from the administration of methimazole, along with other effects including arthralgia, white blood cells problems, mild hepatic injury, emesis, atopic reactions, and headaches [18, 20]. Carbimazole and methimazole are also known to cause cholestasis, according to some reports [21].

2.3. Propylthiouracil *as a Treatment of Graves' Disease*

Among clinicians, the use of propylthiouracil for patients with Graves' disease is often less favored except for some special cases. Propylthiouracil is usually prescribed to patients with low tolerance to the adverse effects of other thionamides, such as women in their first trimester of pregnancy and patients who experience thyroid storms [14]. This drug works by inhibiting the deiodination of thyroxine into triiodothyronine, but that process does not play a significant role except in cases of severe thyrotoxicosis. Other than that, the half of life of this drug is only 90 minutes, which is notably shorter than methimazole that has a half life of 6 hours [21].

In the United States, the use of this drug is strictly limited to patients with strong indications due to its hepatotoxic effects. Patients treated with propylthiouracil are required to have their liver functions monitored and observed [21]. In pediatric settings, it is widely accepted that the administration of propylthiouracil is not recommended mainly because of its hepatotoxic effects [22].

Propylthiouracil also does not work well with radioactive iodine therapy. In a study involving 86 patients who went under radioactive iodine therapy, persistent hyperthyroidism was found significantly higher in those who were pretreated with propylthiouracil. [23]

However, in some cases like Graves' disease in pregnancy, propylthiouracil becomes the first-line treatment. Propylthiouracil crosses the placenta less than methimazole, so this drug is considered to be safer for pregnancy. Compared to methimazole, there are less cases of fetal hypothyroidism and pregnancy complications in propylthiouracil therapy. [24]

2.4. Shared Adverse Effects of Thionamides

Pyrexia, urticaria, and arthralgia are some problems that are considered as minor adverse effects of thionamides. On the other hand, agranulocytosis and Steven Johnson's-like syndrome are considered as the major adverse effects. There is a consensus that requires clinicians to stop administering thionamides if patients start showing at least one major adverse effect. [15]

3. Conclusion

The use of thionamides is so far seen as the most preferred way to treat Graves' disease patients. Among the thionamides themselves, propylthiouracil is less favored than methimazole and carbimazole due to its hepatotoxic effects. However, there are still some special cases where clinicians are obliged to use propylthiouracil instead of other thionamides in the treatment of Graves' disease.

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