

Pediatric Graves' Disease: Controversies in Management

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Key Words

Thyroid · Hyperthyroidism · Methimazole · Propylthiouracil · Radioactive iodine · Thyroidectomy · Hepatotoxicity

Abstract

Background/Aims: Graves' disease (GD) is the most common cause of thyrotoxicosis in children and adolescents. Caused by immunologic stimulation of the thyroid-stimulating hormone receptor, lasting remission occurs in only a minority of pediatric patients with GD, including children treated with antithyroid drugs (ATDs) for many years. Thus the majority of pediatric patients with GD will need thyroidectomy or treatment with radioactive iodine (RAI; ^{131}I). **Results:** When ATDs are used in children, only methimazole should be used. Propylthiouracil is associated with an unacceptable risk of severe liver injury in children and should never be used as first-line therapy. If remission (defined as normal thyroid function off ATDs) is not achieved after 1 or 2 years of ATD therapy, ^{131}I or surgery may be considered, with the choice influenced by the age of the individual. When ^{131}I is used, administered doses should be $>150 \mu\text{Ci/g}$ of thyroid tissue. When surgery is performed, near total or total thyroidectomy is recommended. **Conclusion:** Choosing a treatment approach for childhood GD is often a difficult and highly personal decision. Discussion of the advantages and risks of each therapeutic option is essential to help the patient and family select a treatment option.

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Graves' Disease

Graves' disease (GD) is the most common cause of hyperthyroidism in children and adults, and occurs when the thyroid gland is stimulated by immunoglobulins [1, 2]. In children, the incidence of GD is about 1:10,000 [3]. Hashimoto's thyroiditis has been associated with transient hyperthyroidism, but the relative incidence of this condition to GD in children is not known [4].

Current treatment approaches for GD include the antithyroid drugs (ATDs) propylthiouracil (PTU), methimazole (MMI; or carbimazole which is converted to MMI), surgery, and radioactive iodine (RAI; ^{131}I). These therapies have been used for more than five decades [5–8]. The treatment of GD in children remains controversial, and treatment practices vary widely among institutions and practitioners [9]. Central to considering treatment options in GD in the pediatric population is recognizing that remission occurs in a minority of individuals.

Antithyroid Drugs

PTU and MMI reduce thyroid hormone synthesis by inhibiting the oxidation and organic binding of thyroid iodide [10]. MMI is 10- to 20-fold more potent than PTU and has a longer half-life [10]. Importantly, these medications are not curative. Rather, they palliate the hyperthy-

roid state until it spontaneously resolves or definitive treatment is rendered. Despite the fact that PTU and MMI were introduced long ago and are associated with adverse events (AEs), newer and safer antithyroid medications have yet to be introduced. The risks of ATD drug use, however, can be mitigated by avoiding the use of PTU, which is associated with a risk of liver failure and death in children and adults [11–13], and using relative low doses of MMI.

PTU Hepatotoxicity

In 2008, a number of serious complications related to the use of PTU in children were brought to the attention of the author of this report [14]. In response, a review of AEs related to ATD use in the pediatric population was performed [3]. These AEs were brought to the attention of the US Food and Drug Administration (FDA) and the National Institutes of Health (NIH). In response, a workshop was held at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) on October 28, 2008 to evaluate PTU safety in children. As noted in the minutes of the conference [3], the risk of PTU-induced liver failure leading to transplantation was estimated at 1 in 2,000 children and adolescents. A more detailed analysis of PTU-related risks in children has been recently published [15]. In adults, this risk is estimated to be about 1 in 10,000 individuals [13].

The number of children developing PTU-induced liver injury that was reversible was estimated to be at least 10-fold greater than the number of children who develop liver failure requiring transplantation. Because PTU-induced liver injury is of rapid onset and can be rapidly progressive, biochemical monitoring of liver function tests and transaminase levels is not useful in managing the hepatotoxicity risk in a PTU-treated patient [3]. Considering the risk of PTU-related hepatotoxicity in children, Rivkees and Mattison [12] recommended that the use of PTU be stopped, and children taking the medication should be considered for alternative treatments.

Appropriate Limited Use of PTU

Although PTU use should be avoided in favor of MMI, there is a role for the limited use of PTU. PTU use can be considered in circumstances when neither prompt surgery nor ^{131}I treatments are options when a toxic reaction to MMI and ATD therapy is necessary. In this situation, PTU use should be short term only. Because of potential teratogenic effects of MMI [16], PTU also is the drug of choice during the first trimester of pregnancy [17].

Methimazole

In the USA and many countries, MMI (or carbimazole) is available and should be considered as the drug of choice for GD. The typical MMI dose is 0.2–0.5 mg/kg per day, with a range from 0.1 to 1.0 mg/kg per day [2]. Although many practitioners give MMI in divided administered doses, data do not support a need for such [18].

Although MMI has a better overall safety profile than PTU, MMI is associated with minor AEs [19]. MMI-related AEs include agranulocytosis and allergic reactions. Agranulocytosis has been reported in about 0.3% of adult patients taking MMI or PTU [7, 20, 21]. Agranulocytosis is dose-dependent with MMI, and rarely occurs at low doses [7, 20, 21]. When it develops, agranulocytosis occurs over the first 100 days of therapy in 95% of individuals [7, 20, 21]. If patients taking MMI develop fever, pharyngitis, or feel ill, the medication should be immediately discontinued by the patient, a physician contacted, and a white blood cell count obtained.

Recently, we reviewed the AEs associated with MMI use in our last 100 consecutive pediatric patients treated with this medication [19]. AEs attributed to the use of the medication were seen in nearly 20% of patients, including 3 who developed Stevens-Johnson syndrome, requiring hospitalization in 2 children.

Higher doses of antithyroid medication are sometimes administered continuously and combined with L-thyroxine in doses to maintain euthyroid levels (so-called block-and-replace therapy). However, this approach is not recommended as it has been shown to result in a higher rate of side effects [22]. Because MMI use in children is associated with a low but real risk of minor and major side effects [19], there is no 'safe' ATD [23].

Duration of Therapy

The issue of how long ATDs should be used in children before considering RAI or surgery is a topic of controversy and warrants further study. Prospective studies in adults show that if remission does not occur within 18 months, there is little chance of remission with prolonged therapy [24]. In children, when ATDs are used for 1–2 years, remission rates are generally 20–30% [25–27]. The chance of remission after 2 years of ATDs will be low if the thyroid gland is large (>2.5 normal size for age) [28], the child is young (<12 years) [26, 27, 29], not Caucasian, initial serum TRAb levels are high, or free T_4 levels are high at diagnosis (>4 ng/dl; 50 pmol/l) [27].

Studies of large cohorts of pediatric patients with GD treated with ATDs for extended periods [28, 30] have revealed low remission rates that are comparable to those

seen with 2 years of therapy. Of 120 pediatric patients treated with ATDs at one center, after 1 year of therapy with ATDs, 25% were in remission; after 2 years, 26%; after 4 years, 37%, and after 4–10 years, 15%. Importantly, 30% of the children who went into remission eventually relapsed [30].

When 184 pediatric patients were treated with ATDs for up to 4 years in another report, the overall remission rate was 23% [28]. After 1 year of ATDs, 10% were in remission; after 2 years, 14%; after 3 years, 20%, and after 4 years, 23% were in remission. In another study, 113 patients received ATDs for prolonged periods [31]. After 10 years of treatment, 33% remitted with ATDs [31]. Persistence of GD in children is likely related to the persistence of TRAbs. TRAb levels normalize after 24 months in only 18% of pediatric patients on ATDs in one report [32].

Considering the above data, many practitioners will consider a trial of MMI for 1 or 2 years and proceed to surgery or ^{131}I therapy if remission does not occur. Practitioners may also elect to continue ATDs for many years, as long as toxic reactions and progressive thyromegaly do not occur.

Radioactive Iodine

RAI therapy of GD was introduced more than 60 years ago by Saul Hertz and co-workers at Massachusetts General Hospital, with later contributions coming from Earl Chapman and others [6, 33]. It is estimated that more than 1 million individuals have been treated with ^{131}I for hyperthyroidism [6]. The use of RAI has been reported in more than 1,200 children [8]. Patients as young as 1 year of age have been treated with ^{131}I with excellent outcomes [8]. Overall studies of ^{131}I use in children report remission rates that exceed 95% [8, 34, 35].

The goal of ^{131}I therapy for GD is to induce hypothyroidism. ^{131}I doses are typically calculated to deliver the desired amount of radiation based on gland size and RAI uptake. Alternatively some centers administer all patients the same fixed dose of ^{131}I with excellent outcome [36]. To achieve thyroid ablation or hypothyroidism, $>150\ \mu\text{Ci}$ of ^{131}I per g of thyroid tissue should be administered [37, 38]. With larger glands (30–80 g), higher administered activities of ^{131}I (200–300 μCi of ^{131}I per g) may be needed [37]. RAI is often not effective with large glands ($>80\ \text{g}$) [39]. Thus, surgery may be preferable to ^{131}I in these patients.

Some centers administer a fixed administered dose of about 15 mCi ^{131}I to all children [36] rather than indi-

vidually calculated administered doses. One potential advantage of calculated vs. fixed dosing though is that it may be possible to use lower administered doses of ^{131}I when the administered dose is calculated, especially when uptake is high.

Less than 10% of children complain of mild tenderness over the thyroid in the first week after therapy which can be treated effectively with acetaminophen or non-steroidal anti-inflammatory agents for 24–48 h [35, 37]. There are rare reports of pediatric patients with severe hyperthyroidism who have developed thyroid storm after receiving ^{131}I [40]. Thyroid storm in this setting is believed to reflect progression of the uncontrolled hyperthyroid state. Thus, if T_4 levels are $>20\ \mu\text{g}/\text{dl}$ (200 nmol/l) or free T_4 levels are $>5\ \text{ng}/\text{dl}$ (60 pmol/l), we treat children with MMI until T_4 and/or free T_4 levels normalize before proceeding with ^{131}I therapy [37].

Hypothyroidism typically develops by 2–3 months post-treatment [36, 37]. When administered doses $>150\ \mu\text{Ci}$ of ^{131}I per g of thyroid tissue are administered, hypothyroidism rates are about 95% [2, 8, 23]. If hyperthyroidism persists 4–6 months after therapy, retreatment with ^{131}I is indicated.

Risks of Genetic Damage with RAI

The literature contains data on 500 offspring born to approximately 370 subjects treated with ^{131}I for hyperthyroidism during childhood and adolescence [8]. The incidence of congenital anomalies reported among the offspring of patients treated with RAI does not differ from the incidence in the general population. In addition, there was no increased prevalence of congenital anomalies in the offspring of 77 patients treated for thyroid cancer in childhood with 80–700 mCi of ^{131}I [41]. Thus, long-term genetic damage is not known to be associated with ^{131}I for GD.

Thyroid Neoplasm Risk with RAI

The thyroid gland is unique in its developmental sensitivity to malignancy following low-level radiation exposure [42–44]. When individuals are <20 years of age at the time of low-level thyroid irradiation, thyroid cancer risks increase the younger one is [42–44].

Detractors of ^{131}I therapy point to the increased rates of thyroid cancer and thyroid nodules observed in young children exposed to radiation from nuclear fallout at Hiroshima or after the Chernobyl nuclear reactor explosion [44, 45]. The risk of thyroid neoplasms, however, is greatest with exposure to low-level external radiation (0.1–25 Gy; ~ 0.09 –30 $\mu\text{Ci}/\text{g}$) [42, 44–46], not with the higher

doses used to treat GD. We are not aware of cases of thyroid cancer developing in patients treated with $>150 \mu\text{Ci}$ of ^{131}I per g of thyroid tissue for childhood GD attributable to RAI therapy.

Although RAI is being used in progressively younger ages, we do not know if there is an age below which high-dose ^{131}I therapy should be avoided. Risks of thyroid cancer after external irradiation are highest in children <5 years of age and progressively decline with advancing age [34, 42, 44, 47]. If there is residual thyroid tissue in young children after RAI treatment, there is a theoretical risk of thyroid cancer. Thus, appropriate doses are needed and low doses avoided.

Non-Thyroid Cancer Risks with RAI

In addition to thyroid cancer risks, potential influences of ^{131}I therapy on other cancers need to be considered. This issue has been examined in several large cohorts of adults in the USA and other countries. These studies have not revealed increased cancer incidence or mortality in adults treated with ^{131}I for GD [48–54].

In comparison with the studies in adults, few studies have focused on populations exposed to ^{131}I in childhood for the treatment of GD. The longest follow-up study of pediatric patients involved 36-year outcomes of 116 patients who were <20 years of age when treated with ^{131}I between 1953 and 1973 [34]. This group did not have an increased cancer rate.

Total-body radiation dose after ^{131}I varies with age, and the same absolute dose of ^{131}I will result in more radiation exposure to a young child than to an adolescent or adult [55, 56]. At present, we do not have dosimetry information regarding ^{131}I use in children with GD to assess total body exposure in children. Based on phantom modeling, it has been estimated that at 0, 1, 5, 10, 15 years of age, and adulthood, respective total body radiation doses are 11.1, 4.6, 2.4, 1.45, 0.90, and 0.85 rem (0.01 Sv) per mCi of ^{131}I administered [55, 56]. Based on the Biological Effects of Ionizing Radiation Committee V (BEIR VII) analysis of acute, low-level radiation exposure [57], the theoretical lifetime attributable risk of all cancer incidence and all cancer mortality can be estimated based on theoretical calculations. Based on these estimates we feel it is prudent to avoid RAI therapy in very young children (<5 years) and to avoid >10 mCi in patients <10 years of age. It is important to emphasize that these recommendations are based on theoretical concerns and not 'hard data'; further study of this issue is needed.

It is important to recognize that there may be circumstances in which ^{131}I therapy is required in young chil-

dren. This situation may occur when a child has developed a reaction to antithyroid medications, proper surgical expertise is not available, or the patient is not a suitable surgical candidate.

Surgery

Surgery is an acceptable form of therapy for GD in children [9]. When performed, near total or total thyroidectomy is recommended, as subtotal thyroidectomy is associated with a higher relapse rate [58]. Surgery is preferred in young children (<5 years) when definitive therapy is required and can be performed by an experienced thyroid surgeon. In individuals with large thyroid glands (>80 g), the response to ^{131}I may be poor [39, 59] and surgery is recommended for these patients.

Data in adults show that acute complications following thyroidectomy include hypocalcemia (40%), hematoma (2%), and recurrent laryngeal nerve paresis (2%) [60, 61]. Long-term complications include hypoparathyroidism (1%) and recurrent laryngeal nerve injury (2%). Although surgery is performed in children with GD, relatively little is known about pediatric surgical outcomes and complication data from adults have been improperly applied to the pediatric population [9].

To address this issue, a cross-sectional analysis of Healthcare Cost and Utilization Project – National Inpatient Sample hospital discharge information from 1999 to 2005 was performed by our group. Children aged 0–6 years had complication rates of 22%, those aged 7–12 years had complication rates of 11%, and those aged 13–17 years had complication rates of 11%. These rates are higher than those seen in adults. Importantly, when surgery was performed by pediatric surgeons, the complication rate for total thyroidectomy (not for cancer) was about 15%. In comparison, the complication rate for high-volume (>30 thyroidectomies per year) thyroid surgeons was about 4% ($p < 0.01$). Thus, surgery may not be an optimal option for some pediatric patients with GD, especially in young children. Considering these data, in circumstances where local pediatric thyroid surgery expertise is not available, referral of a child with GD to a high-volume thyroid surgery center of excellence that has pediatric experience is indicated.

Stratification of Treatment Approaches for Children

Based on what is known about the risks of different treatments and the pathogenesis of GD, we can be more selective in our approach to therapy. To reduce treatment

risks and expedite cure, the treatment options can be guided by the patient's age and the nature of the intrinsic autoimmune disease.

In determining if drug therapy is likely to be successful, TRAb levels and thyroid size may be predictive of remission rates. In situations where the thyroid gland is large, ultrasonography is useful in assessing gland size, which can be underestimated. Ultrasonography may also help to identify children with hyperthyroidism due to hyperfunctioning nodules versus GD. The presence of low TRAb levels and a small thyroid suggests the possibility of remission on medical therapy. Yet, if TRAb levels are high and the thyroid is large, the odds of spontaneous remission are low [62, 63]. However, TRAb levels and thyroid size may not always be indicative of remission likelihood.

It is important to emphasize that when ATDs are used, only MMI should be used. When RAI is used, it is important that appropriate doses of ^{131}I be administered in children. In general, doses of ^{131}I $>150 \mu\text{Ci/g}$ of thyroid tissue are needed, with higher doses needed with larger glands. When surgery is performed, total thyroidectomy is the procedure of choice and due to the higher complication rate in children than adults, surgery by an experienced thyroid surgeon is essential.

For children <5 years of age, we consider MMI as a first-line therapy. Because young children are less likely to have remission than older children on drug treatment [26, 29], prolonged drug therapy may be needed. If there are no toxic effects, continuing MMI is reasonable until the child is considered old enough for RAI therapy. Alternatively, thyroidectomy or ablative RAI therapy can be considered if reactions to medications develop or there is the desire to avoid prolonged drug use.

Fifteen percent of children with GD will present between 6 and 10 years of age [64]. Considering MMI therapy as a first-line measure for this age group is reasonable. Yet, as 10 years of age are approached, either drug therapy can be considered as initial therapy if prognostic factors suggest potential likelihood of remission, and RAI or drug therapy can be considered initially if the chance of spontaneous remission appears slim.

Children 10 years of age and older account for 80% of the pediatric cases of GD. For this age group, RAI or MMI can be considered as first-line treatment options depending on remission prognostic factors. In addition, teenage females need to be cautioned about the potential risks of GD and GD therapy on the fetus and that TRAb levels may persist after definitive treatment and pose a risk to future pregnancies.

Finally, irrespective of the treatment option selected, careful follow-up is needed for all patients treated for GD. Long-term follow-up should include regular examination of the thyroid gland and measurement of circulating levels of thyroid hormones once or twice a year. All newly appearing thyroid nodules should be biopsied or excised.

Choosing a treatment approach for childhood GD is often a difficult and highly personal decision. Discussion of the advantages and risks of each therapeutic option by the physician is essential to help the patient and family select a treatment option.

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