

CONTROVERSY IN CLINICAL ENDOCRINOLOGY

An Optimal Treatment for Pediatric Graves' Disease Is Radioiodine

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Context: Antithyroid medications, surgery, and radioactive iodine have been used for more than five decades for the treatment of hyperthyroidism due to Graves' disease in children, adolescents, and adults. Despite the widespread use of these different approaches, controversy still exists relative to the merits of each treatment, especially regarding the use of radioactive iodine.

Objective: The objective of the study was to address the risk and benefits of ^{131}I therapy, as compared with other treatment approaches.

Position: Long-term, spontaneous remission of Graves' disease occurs in less than 30% of children. Thus, the majority of children with Graves' disease will need definitive, curative therapy. There is little evidence that use of antithyroid medications beyond 1 or 2 yr in-

creases the likelihood of spontaneous, long-term remission. Although the use of antithyroid medications is standard practice, the use of antithyroid medications involves definite risks. When used at sufficient doses, radioactive iodine is an effective cure for Graves' disease and is associated with few acute side effects. Potential long-term adverse side effects, including thyroid cancer and genetic damage, have yet to be observed in individuals treated as children or adolescents with ^{131}I .

Conclusion: Properly administered, radioactive iodine remains an ideal form of treatment for Graves' disease in the pediatric population. Because of the increased risk of thyroid cancer associated with low-dose thyroid irradiation in children, larger, rather than smaller, doses of ^{131}I should be given. (*J Clin Endocrinol Metab* 92: 797–800, 2007)

GRAVES' DISEASE IS the most common cause of hyperthyroidism in the pediatric population, peaking in late childhood with a strong female-to-male predominance (1, 2). Current treatment approaches involve antithyroid medications, surgery, and radioactive iodine, and these have been used for more than five decades (3–8).

Central to considering treatment options in Graves' disease in the pediatric population is recognition of the fact that remission occurs in the minority of individuals. The most extensive study of this issue involving nearly 200 children showed that less than 20% of children treated medically achieved remission lasting more than 2 yr (9). In another large series of 186 children, less than 30% of children went into remission (10). Remission rates are even less in prepubertal than pubertal children, reaching only 15% of prepubescent children (11, 12). Presently it is not possible to accurately identify the small percentage of children who will achieve lasting remission, although remission is more likely when the thyroid is small at initial presentation (10). Compliance-related issues may also contribute to the prolonged hyperthyroid state, which is especially true when propylthiouracil (PTU) is prescribed to be taken several times per day *vs.* methimazole (MMI) prescribed once per day (13).

When spontaneous remission of Graves' disease does not

occur, prolonged drug therapy will control the hyperthyroid state; however, prolonged antithyroid drug therapy does not appear to increase the likelihood of lasting remission. More than two decades ago, Greer *et al.* (14) showed that the likelihood of remission of hyperthyroidism was similar when antithyroid medications were used for 6 or 36 months. Most recently, Weetman (15) reviewed prospective trials comparing different durations of treatment in adult subjects, which collectively show that rates of remission are not improved with antithyroid drug therapy beyond 18 months in adults.

An important concern related to antithyroid drug use in children is the occurrence of adverse side effects. Up to 25% of children will have minor side effects, including pruritus, hives, myalgias, small increases in liver enzymes, and leukopenia (8, 16). Up to 0.5% of PTU- or MMI-treated children will develop serious complications (8, 16).

By 1998, 36 serious adverse events and two deaths from liver failure (from PTU) due to antithyroid drug therapy of childhood Graves' disease had been reported to the U.S. Food and Drug Administration MedWatch program, which is very prone to underreporting (8). Several other deaths related to antithyroid medication therapy in children have been reported to one of the authors (S.A.R.) by professionals, including PTU-related liver failure and MMI-related bone marrow failure.

Due to the lack of a centralized registry to monitor and track side effects to antithyroid medications, we do not have reliable estimates of scope and seriousness of complications

Abbreviations: MMI, Methimazole; PTU, propylthiouracil.

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from Graves' disease therapy in children. Published data about the risks of continuing medical therapy or changing to another medication after the occurrence of toxic reactions in children are limited, as well. Considering the frequency of minor and major side effects, physicians will thus unexpectedly need to opt for alternative medications or definitive treatment in the midst of a course of drug therapy.

Surgery is the oldest form of definitive therapy of Graves' disease, with the Nobel Prize in Physiology and Medicine awarded to Kocker in 1909 for developments in this area. The higher relapse rates seen with subtotal thyroidectomy have resulted in the recommendation that total thyroidectomy be the surgical procedure of choice for Graves' disease (17–19). Although it can take several months for the hyperthyroid state to remit after ^{131}I treatment, the hyperthyroid state remits very quickly after surgery.

Acute complications after surgery in adults include hypocalcaemia (40%), hematoma (2%), and recurrent laryngeal nerve paresis (2%) (17, 18, 20, 21). Long-term complications include hypoparathyroidism (1%) and recurrent laryngeal nerve injury (2%) (22). Although not mentioned as a complication, surgery is universally associated with neck scars, which teenagers and young adults often try to hide with necklaces, scarves, and high collars. Hypertrophic scars after thyroidectomy, requiring medical or surgical treatment, occur as well. Associated with surgery are postoperative pain and discomfort and time lost from school and activities. Surgery is expensive, with collective costs of thyroidectomy often topping \$7000.

Of critical importance in evaluating surgical outcome of Graves' disease is the experience of the surgical center and surgeon. The thyroidectomy complication rates noted pertain to expert surgical centers. We know little about thyroidectomy complications when surgery was performed by non-endocrine surgeons, and there are no comprehensive studies that have evaluated complication rates of thyroidectomy for Graves' disease in children.

Radioactive iodine therapy of Graves' disease was introduced more than 60 yr ago, and it is estimated that more than one million individuals have been treated with ^{131}I for hyperthyroidism (5). The use of radioactive iodine has been detailed for more than 1200 children (8). Patients as young as 1 yr of age have been treated with ^{131}I with excellent outcomes (8). These studies have reported remission rates that exceed 95%, with very rare complications (8, 23, 24).

^{131}I doses are typically calculated to deliver the desired amount of radiation based on gland size and radioactive iodine uptake (25). Some centers administer to all patients the same fixed dose of ^{131}I with excellent outcome (26). When children are treated with more than 200–250 Gy (~ 220 to 275 $\mu\text{Ci/g}$), hypothyroidism is achieved in nearly 95% of patients (27). Gland size also influences treatment outcome, as higher doses of ^{131}I are needed to induce hypothyroidism when large glands are present (up to 60 g) (27). When thyroid size exceeds 80 g, remission rates after ^{131}I therapy are poor (28). Thus, surgery is preferred when thyroid gland size is large (>60 –80 g).

Few acute adverse responses to ^{131}I therapy of Graves' disease have been described (8, 24). In adults, transient nausea has been reported after radioiodine administration, and

mild pain over the thyroid gland may develop 1 to 3 d after a therapeutic dose (29). These side effects are self-limited and respond to treatment with nonsteroidal antiinflammatory agents.

Thyroid storm has been reported rarely to develop 1–14 d after ^{131}I treatment (24, 30, 31), with patients with severe thyrotoxicosis and very large goiters at highest risk. If antithyroid medication is stopped too soon before treatment with ^{131}I and the thyroid is large, thyroid hormone stores will be replenished and increase the risk for thyroid storm (31). Discontinuing antithyroid medication 5 d before ^{131}I is administered is sufficient (32). Symptoms of hyperthyroidism can be readily controlled when antithyroid medication is stopped by β -blocker therapy.

Although the potential of worsening ophthalmopathy has been reported in a small percentage of adults who have received ^{131}I (33), this is an uncommon problem in children. In prospective studies of children, worsening of eye disease has not been observed after ^{131}I therapy (34). When profound Graves' ophthalmopathy is present, adjunctive prednisone therapy for 3 months has been shown to prevent the worsening of eye disease after ^{131}I (35). Although it was suggested that ^{131}I therapy was associated with the subsequent hyperparathyroidism, case-controlled studies dispute this notion (36, 37).

The thyroid gland is unique in its developmental sensitivity to malignancy after radiation exposure. Individuals older than 20 yr of age do not have an increased risk of thyroid cancer when exposed to low-level thyroid irradiation (38–41). Yet, when individuals are younger than 20 yr of age at the time of low-level thyroid irradiation, thyroid cancer risk increases the younger the person is (38–40).

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. However, these data do not directly apply when assessing risks of ^{131}I therapy. The risk of thyroid neoplasms is greatest with exposure to low level external radiation (0.1–25 Gy; ~ 0.09 –30 $\mu\text{Ci/g}$) (38–42), not with the higher doses used to treat Graves' disease. It is also important to note that iodine deficiency and exposure to nuclides other than ^{131}I may have contributed to the increased risk of thyroid cancer in the young after the Chernobyl reactor explosion (38, 39, 41). Supporting this concept, thyroid cancer rates were not increased in more than 3000 children exposed to ^{131}I at the Hanford nuclear reactor site in an iodine replete region (43). Increased thyroid cancer rates were also not seen in 6000 children who received ^{131}I diagnostically (39, 44).

The Cooperative Thyrotoxicosis Therapy Follow-up Study also showed that thyroid neoplasms developed in children treated with lower, rather than higher, doses of ^{131}I . Thyroid adenomas developed in 30% of 30 children treated in one center with low doses of ^{131}I estimated to result in thyroid exposure of 25 Gy (~ 30 $\mu\text{Ci/g}$) (45, 46). Yet when children were treated with higher doses of ^{131}I (100–200 Gy; 110–220 $\mu\text{Ci/g}$), the incidence of thyroid neoplasms was not increased (45).

Antithyroid drugs are preferred to radioactive iodine therapy by some clinicians, assuming that thyroid cancer risk is

less after drug therapy than after radioactive iodine. The Cooperative Thyrotoxicosis Therapy Follow-up Study, however, found that the incidence of thyroid carcinomas in more than 10–20 yr of follow-up was 5-fold higher in individuals treated with thioamide drugs than in patients treated with ^{131}I , and it was 8-fold higher than in patients treated surgically (45).

Outcomes after ^{131}I treatment of more than 1200 children and adolescents treated with higher doses of radioiodine for Graves' disease have been reported (8). The duration of follow-up in these studies ranged from less than 5 yr to 15 yr, with some subjects followed for more than 20 yr. These studies have not revealed an increased risk of thyroid malignancy. The longest follow-up studies of children recently treated with ^{131}I come from Read *et al.* (23). When more than 100 patients were surveyed nearly four decades after receiving radioactive iodine, no adverse events or deaths could be attributed to ^{131}I therapy (23).

We are aware of a few reported cases of thyroid malignancy in children previously treated with ^{131}I (5 yr of age at treatment with 50 $\mu\text{Ci/g}$; 9 yr of age at treatment with 5.4 mCi; 11 yr of age at treatment with 1.25 mCi; 16 yr of age at treatment with 3.2 mCi) (8). These individuals were treated with low doses of ^{131}I . We are not aware of thyroid cancer in patients treated with more than 150 Gy (160 $\mu\text{Ci/g}$) of radioactive iodine for childhood Graves' disease attributable to radioactive iodine therapy. Because of the increased risk of thyroid cancer associated with low-dose thyroid irradiation in children, larger rather than smaller doses of ^{131}I should be used.

Although radioactive iodine 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 younger than 5 yr of age and progressively decline with advancing age (23, 39, 41, 47). If there is residual thyroid tissue in young children after radioactive iodine treatment, there is a theoretical risk of thyroid cancer. It may therefore be prudent to avoid radioactive iodine therapy in children younger than 5 yr.

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 radioiodine 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 (48). There is no evidence of an increased rate of birth defects in survivors of the Hiroshima and Nagasaki atomic bomb blasts who were exposed to higher levels of external irradiation of the gonads than are associated with radioactive iodine therapy (49, 50).

In addition to thyroid cancer, potential influences of ^{131}I therapy on other cancers need to be considered. Follow-up from the large cohort of the Cooperative Thyrotoxicosis Therapy Follow-Up Study did not find increased risks of leukemia in the ^{131}I -treated group, as compared with the drug- and surgery-treated groups (51). No increase in overall cancer mortality was seen in the ^{131}I -treated patients either

(52). In one other study, excess thyroid cancer mortality after ^{131}I therapy for Graves' disease was observed during early, but not late, follow-up (53). Yet this was related to increased cancer surveillance and detection, not ^{131}I effects (53).

Total-body radiation doses after ^{131}I vary 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 (27, 54, 55). At 0, 1, 5, 10, and 15 yr of age and in adulthood, respective total body radiation doses are 11.1, 4.6, 2.4, 1.45, 0.90, and 0.85 rem per mCi of ^{131}I (55). Based on the Biological Effects of Ionizing Radiation Committee V (BEIR V) analysis of external radiation exposure, the theoretical risk of cancer death after acute radiation exposure is 0.16% per rem for children and 0.08% per rem for adults, although there is uncertainty associated with these projections (56–58). At present, we do not have good dosimetry information regarding ^{131}I use in children with Graves' disease to assess actual total body exposure and the long-term theoretical risks associated with this exposure, especially in young children.

The past 50 yr of treatment of Graves' disease in children has taught us many lessons. We now know that the majority of children and adolescents with Graves' disease will need definitive therapy, which can be capably achieved by surgery or radioactive iodine. Nevertheless, it is not uncommon for physicians to prescribe prolonged drug therapy, placing the child at continued and possibly increased risk of adverse effects of antithyroid medications. The issue of how long is too long and how we can best monitor and minimize potential toxic effects of antithyroid medication is one of the most important issues facing clinicians treating children with Graves' disease, and it dwarfs the debate of radioactive iodine *vs.* surgery. Operative mortality these days is rare, and we are not aware of any deaths directly related to the use of ^{131}I for the treatment of hyperthyroidism caused by Graves' disease in children. However, serious and fatal adverse events occur with antithyroid drug therapy, which, although uncommon, are not rare enough. New antithyroid medications with lower toxicity profiles than current antithyroid drugs (especially PTU) for the pediatric population are needed.

When considering definitive therapy, we have ample data that address the long-term outcome of radioactive iodine therapy in children. These data have yet to reveal substantive acute or long-term consequences of this method of selective thyroid ablation. Properly administered, radioactive iodine remains an ideal form of treatment for Graves' disease in the pediatric population.

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