

Iodine-131: Optimal Therapy for Hyperthyroidism in Children and Adolescents?

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To assess the medium- to long-term effects of I-131 therapy of hyperthyroidism in children and adolescents, we studied 51 patients (age range 6–18; 8 boys, 43 girls) treated with I-131 for Graves' disease with hyperthyroidism at the University of Michigan Medical Center (1951–1972). Patients received total doses ranging from 3 to 81.6 mCi. The mean followup period was 14.6 ± 7.9 yr. Hyperthyroidism was effectively treated in 49 within 1 to 12 mo. One patient failed to respond to three treatment doses, and hyperthyroidism recurred in two patients: 2 and 11 yr after initial therapy. Of these three patients, two were treated by thyroidectomy and one was retreated successfully with I-131. There were no cases of thyroid cancer, other malignancies or leukemia. The patients' reproductive histories and the health of their offspring were as in the general population. At the time of study, the prevalence of hypothyroidism was 92%, with no recurrent goiters or thyroid nodules. Iodine-131 is found to be safe and effective treatment of hyperthyroidism in children and adolescents and should be the preferred mode of therapy.

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The carcinogenic potential of x-irradiation to the head and neck of children has been emphasized by both the medical profession and the media (1–3). The justified concern on the part of such patients and their physicians has spread to other forms of irradiation used in diagnosis and therapy, such as radioiodine treatment of hyperthyroidism in children. Long-term followup studies of hyperthyroid children treated with radioiodine have been scarce, with the total number of children reported being less than 350 (4–11). The use of radioiodine to treat hyperthyroidism in children remains restricted in many centers for fear of the possibility of irradiation-induced carcinogenesis. Such concern over the

possibility of long-term untoward effects from I-131 is a major factor influencing the selection of a mode of therapy for the individual child, and has led to what we believe is less-than-optimal therapy in many children.

To assess the medium- to long-term effects of I-131 therapy in children with hyperthyroidism, we evaluated 51 children and adolescents treated at our medical center from 1951 to 1972 with attention to the following points: a) efficacy of I-131 in terminating hyperthyroidism, b) prevalence of hypothyroidism after I-131, c) presence of carcinoma, leukemia, or benign thyroid nodules, d) reproductive history of patients after I-131, and e) health of the progeny of these patients.

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MATERIALS AND METHODS

Review of our clinic's records revealed 51 pa-

tients who fulfilled the following criteria: a) age of 18 yr or younger at the time of radioiodine treatment; b) the diagnosis of Graves' disease with hyperthyroidism, established by the presence of characteristic clinical and laboratory findings; and c) a follow-up period of at least 5 yr after treatment. All were examined by one of us (JEF, MDG, or JCS) or by their personal physician within 1 yr of the initiation of this study.

Serum TSH and serum T₄ (radioimmunoassay or CPB) concentrations were obtained for all patients not receiving thyroid hormone replacement at the time of study. A serum T₄ level was determined for all patients on thyroid hormone replacement, and the serum TSH was measured in patients in whom adequacy of replacement therapy was questioned. No attempt was made to discontinue thyroid medication in those 44 patients on replacement at the start of the study.

A complete blood count was determined in any patient with a history or physical examination suggestive of hematopoietic dysfunction (15/51). The reproductive histories of all patients were evaluated, with infertility defined as the failure to conceive after 1 yr of unprotected exposure.

RESULTS

Eight patients had been treated initially with subtotal thyroidectomy for their hyperthyroidism. Forty-four patients (86%) received either propylthiouracil or methimazole for 2–60 mo before I-131 therapy. Any antithyroid drug therapy was discontinued a minimum of 3 days before I-131 therapy and was resumed 5–7 days after I-131 therapy in five patients. The ages at the time of initial I-131 treatment are shown in Table 1. Thirty-seven patients received one dose of I-131, 12 patients two doses, one patient three doses, and one patient four doses. The mean total dose was 14.1 ± 12.4 mCi (range 3.0–81.6) calculated to deliver 100–150 μ Ci of I-131 per gram of thyroid (corrected for 24-hr RAI uptake). Specific information regarding the 14 patients who required multiple doses is presented in Table 2. There are insufficient data to determine the number of rads delivered to the thyroid.

Hyperthyroidism was controlled in 4.8 ± 3.8 mo by I-131 therapy in 49 of 51 patients (96%). One patient failed to respond to three doses (32.1 mCi total); her hyperthyroidism was relieved only after subtotal thyroidectomy. One patient was euthyroid after the initial I-131 dose, but hyperthyroidism recurred 2 yr later and she had a thyroidectomy at another center. Another patient had recurrence of her hyperthyroidism 11 yr after her initial I-131 therapy, but was rendered euthyroid with a second dose of I-131.

TABLE 1. AGE OF PATIENTS AT TIME OF INITIAL I-131 THERAPY

Age (yr)	No. of patients
6–9	2
10–12	2
13–15	8
16–18	39
Total	51

TABLE 2.

Patient	Age	Sex	Goiter (g)	I-131 Doses (mCi)
1	18	F	50	6.2, 5.5
2	18	M	40	4.5, 10
3	18	F	80	13, 10
4	16	F	75	11, 17.7
5	16	F	70	11.3, 14.5
6	16	F	60	11.2, 5
*7	18	F	50	8, 11.7, 12.4
8	16	F	80	11.5, 14.2, 26.9, 29
9	17	F	60	9.1, 10.1
10	17	F	70	11, 13
11	16	F	80	15, 10
12	12	F	60	10, 16.1, 24.8
13	16	F	100	7, 9.9
14	17	F	60	10, 10

* Treatment failure

The mean follow-up period was 14.6 ± 7.9 yr (range 5–27). The prevalence of hypothyroidism 6 mo after treatment was 47% (24/51) and at the time of this study was 92% (47/51), with only seven of 51 not receiving thyroid replacement. Three of these seven manifested hypothyroidism as demonstrated by elevated serum TSH and subnormal serum T₄ values. Although a few of the patients taking thyroid replacement at the time of study may retain residual thyroid function, it is unlikely that they could sustain euthyroidism without therapy; accordingly, a decision was made not to withdraw hormone replacement. No patient was found to have a goiter or palpable nodules.

Twenty-seven patients (53%) had Graves' ophthalmopathy (grades II–III) at the time of initial treatment. No patient had progression of eye disease following I-131 therapy, and onset of eye disease after this therapy was not observed. Improvement in ocular symptoms occurred in 85%, with chemosis and/or lid swelling decreasing in 15/18 (83%). Reductions of 2 mm or more in Hertel exophthalmometer readings were seen in 12/18 (66%). In the other nine patients, ocular data were insufficient to assess degree of improvement.

There were no leukemias, thyroid carcinomas, or other malignancies noted in the patients or their progeny.

TABLE 3. REPRODUCTIVE HISTORIES OF PATIENTS AFTER I-131 THERAPY

Married, > 1 yr, with children	25
Married one year without children	4*
Married, using contraception	8
Single	14
Total	51

* Two are childless for reasons unrelated to I-131.

The patients had a total of 61 pregnancies. There were 60 live births (37 males, 23 females) and one spontaneous abortion. Thirty-nine of these children were examined by us or by their personal physicians within the past year. The other 21 children are healthy according to the parents and any medical information obtainable. Of these 60 children, two have learning disabilities and one has congenital cryptorchidism.

One patient was treated with I-131 (9.9 mCi) 2–3 wk after conception. The child was normal at birth and when studied at 5 years of age.

Of our 29 couples not using contraception, 25 are married and have children (Table 3). Two are childless for irrelevant reasons (azoospermia; hysterectomy), but two others have been married for more than a year, are not using contraceptives, and have not conceived. Fertility studies have not been performed.

DISCUSSION

In this series of 51 patients, hyperthyroidism was effectively controlled in 50. There were two cases of recurrence. One patient responded readily to a second dose of I-131, and the other patient was treated by thyroidectomy at another institution.

The 92% prevalence of hypothyroidism in this study, as a late sequela of I-131 therapy, is somewhat higher than that reported in other series involving I-131 therapy in children and adults (8,12,13). None of our four patients who are still euthyroid has been followed for more than 8 yr. The goal of permanent cure of hyperthyroidism—yet prevention of hypothyroidism—is attainable in probably only a small percentage of children, regardless of whether I-131 or surgery is used as therapy. Antithyroid drugs may not be the answer, for the incidence of permanent remissions appears to be decreasing steadily (14). We have preferred to err on the side of giving more I-131 than less to terminate the hyperthyroid state as quickly as possible (73% relief from hyperthyroidism at 6 mo). By clinical and laboratory evaluations, hypothyroidism is readily detectable and easily treated. However, prolonged follow-up will be necessary to detect its insidious onset in some.

No thyroid nodules, thyroid cancer, leukemia, decreased fertility, or evidence of genetic damage has occurred. The lack of thyroid nodules in our patient population is possibly due to the larger doses of I-131 (3–81 mCi) used as compared with Sheline's (4), and to the use of thyroid replacement in many patients, thereby preventing TSH stimulation of residual tissue. Larger doses of I-131 may also protect the child from the possibility of thyroid cancer induction, perhaps because this dose destroys the ability of the follicular cell to replicate. The literature reports that thyroid cancer has occurred in two children treated with I-131 for hyperthyroidism (15,16). One child developed thyroid cancer within 27 mo of therapy; this relatively brief interval suggests that the cancer was present at the time of I-131 therapy. The other child received three small doses of I-131—barely sufficient to control her hyperthyroidism—over a 4-yr period; then, 4 yr later, she underwent thyroidectomy for a recurrent nodular goiter. At operation, an invasive adenoma of unstated size was found, together with multiple benign adenomas. Whether this was simply a microscopic finding or was of clinical significance is not known.

No leukemia was detected in our patient series, although the possibility of subclinical disease exists, since complete blood counts were not obtained in all patients. However, no case of leukemia after I-131 therapy has been reported in children to date, and this disorder is not likely to remain subclinical for long in children and young adults (5–11).

The fear of I-131-induced infertility—or of genetic damage to the progeny of I-131-treated children—persists, though no increase in infertility, in congenital abnormalities, or in spontaneous abortions has been reported. Recent information reported by Robertson et al. indicates that the gonadal radiation dose from a 10-mCi therapy dose may be no more than that received from such common radiologic procedures as IVP or barium enema (17). The infertility rate in our series is not different from that of the general population (18), and none of the infertile patients received more than 12 mCi. Sarkar et al. were not able to demonstrate any effect on fertility, or any evidence of genetic damage, in their children treated for thyroid cancer with a mean total dose of 196 mCi, as compared with 14.6 mCi in our group (19).

We believe that I-131 therapy of hyperthyroidism in children is safe and effective and that it should be the preferred mode of treatment. The theoretical risks of such therapy have not been realized in the clinical setting. Even if these theoretical risks were realized, they would have to be weighed against the real risks incurred by thyroidectomy in such chil-

dren. Some thyroid surgeons are now advocating total thyroidectomy in children less than 10 years of age to decrease the rate of recurrence (20,21); the extent of such an operation must add to the morbidity rate in thyroidectomies.

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