CLINICAL STUDY

Optimized radioiodine therapy of Graves’ disease: analysis of the delivered dose and of other possible factors affecting outcome

Bogdan Catargi, Frédéric Leprat, Martine Guyot1, Nathalie Valli1, Dominique Ducassou1 and Antoine Tabarin
Department of Endocrinology and 1Department of Nuclear Medicine, University Hospital of Bordeaux, Bordeaux, France
(Correspondence should be addressed to B Catargi, Hopital Haut-Leveque, Avenue de Magellan, 33 604 Pessac, France)

Abstract
The best approach to radioiodine dose selection in the treatment of Graves’ hyperthyroidism remains highly controversial. The formula to calculate the individual dose of 131I to be delivered has been used for half a century and takes into account the thyroid mass, the effective half-life and the maximum uptake of 131I. The objective of the present study was to evaluate the accuracy of this formula by determining the relationship between the administered dose of 131I calculated to deliver a target dose of 50 Gy to the thyroid and the actual exact organ dose. We further analyzed if therapeutic success, defined by euthyroidism following the individually calculated dose, can be predicted by different pretreatment parameters and particularly by organ dose.

One hundred patients with a first episode of Graves’ disease and who had received optimal thyroid irradiation after precise dosimetry were retrospectively reviewed. The patients were categorized according to their thyroid function (plasma free thyroxine (T4) serum concentration) as eu-, hyper-or hypothyroid during and 1 year after treatment. The relationship between the administered dose and organ dose was assessed by simple regression. We compared free T4, free tri-iodothyronine, thyroid weight, the number of patients with antithyroperoxidase antibodies and TSH receptor autoantibodies, 24 h urinary iodine excretion, 131I uptake, and the exact dose of 131I delivered to the thyroid as pretreatment variables. Although we found a correlation between administered dose (mCi) and organ dose (Gy) ($r = 0.3, P = 0.003$), the mean coefficient of variation for organ dose was 45%. Individualized radioiodine therapy enabled euthyroidism in 26% of patients and failed in 74% of patients (33% had persistent or recurrent hyperthyroidism and 41% permanent hypothyroidism). 131I uptake was significantly higher in the hyperthyroidism group in comparison with the euthyroid group. However, organ dose and other pretreatment variables did not differ among the three groups.

In conclusion, these results confirm the low performance of individual dosimetry using what are established ratios, since the delivered dose to the gland, although correlated to the intended dose, is highly variable. The finding that other usual pretreatment variables are not different between groups, gives little hope for improving the way of calculating the ideal dose of radioiodine. We suggest to those not yet ready to give a standard or an ablative dose for Graves’ hyperthyroidism that they abandon this way to calculate the 131I dose.

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Introduction
Graves’ disease (GD) is an autoimmune disorder in which thyroid-stimulating hormone receptor antibodies cause the thyroid gland to synthesize and release large amounts of thyroid hormones. The three, not entirely satisfactory, treatment modalities are antithyroid drugs, radioiodine and partial thyroidectomy. Radioiodine is increasingly used as the treatment of choice in most patients with Graves’ hyperthyroidism because of its ease, low cost and low rate of complications (1). As the effect is to a large extent dependent on the dose of 131I radiation absorbed, much controversy arises about whether hypothyroidism following radioiodine therapy is a complication or not. Because of the availability of sensitive and specific assays to diagnose hypothyroidism at an early phase and adjust thyroid hormone replacement, some authors do consider hypothyroidism as an endpoint rather than a complication, and apply standard radioiodine activities (2). Conversely, overtreatment means unnecessary radiation exposure for the patient and for the environment, and therefore the optimal concept is application of a disease-determined dose (3). With an ideal intermediate radiation dose the number...
of hyper- as well as hypothyroid patients should be low, leaving the highest percentage of cases euthyroid. However, no exact mathematical relationship has been found between $^{131}$I dose and the appearance of hyperthyroidism or relapse of hyperthyroidism (4). The difficulty in calculating exactly the individual radiation dose to the thyroid is explained by the necessity to determine at least three unknowns: thyroid volume, maximum uptake and effective half-life of the administered activity (5). Furthermore, outcome depends also on the autoimmune nature of the disease (6) and pre- or post-treatment with antithyroid drugs (7, 8).

The literature dealing with calculation of the $^{131}$I dose is overwhelming, but few studies have reported accurate determination of factors that enable calculation of the therapeutic activity, the exact organ dose and the possible role of additional factors influencing outcome after first $^{131}$I treatment. The aim of the present study was: (i) to establish the reliability between the administered radioiodine dose and the actual radiation dose delivered, and (ii) to further determine the possible influence of pretreatment factors other than organ dose for outcome in 100 patients with GD treated with an individually optimized dose of $^{131}$I.

**Patients and methods**

**Patients**

One hundred patients with first hyperthyroid GD episode (aged 52.0 ± 11.7(S.D.): 89 women and 11 men) who were treated for the first time with $^{131}$I in our care unit between 1987 and 1994 were studied in 1995. As other factors may influence the results of radioiodine treatment, our study concerned only patients without antithyroid drug therapy, and with no excessive 24 h iodine excretion. Diagnosis of hyperthyroidism due to GD was based on two or more of the following criteria: specific clinical findings; high diffuse uptake on radioisotope scintigraphy; and positive immunological markers. Fifty patients out of 88 had elevated TSH receptor autoantibody (rTSHAb) levels ranging from 13 to 180 IU/ml, and 67 out of 99 had elevated antithyroidperoxidase antibodies (TPOAb) ranging from 103 to 37 190 IU/ml.

**Methods**

rTSHAb and TPOAb were measured also using Immunootech kits (normal range <10 IU/ml and <100 IU/ml respectively). The 24 h iodine urinary excretion was determined by the colorimetric ceric–arsenic assay (Technicon, Tarrytown, NY, USA; normal range in our area 40–400 g/24 h) in each patient before $^{131}$I administration.

**Dose determination**

The therapeutic activity administered (A) was calculated to deliver a predetermined target dose of 50 Gy according to a modified Marinelli formula (9):

$$A (\text{mCi}) = \frac{\text{Constant} \times \text{target dose (Gy)} \times \text{thyroid weight (g)}}{C (\%) \times T (\text{days})}$$

where $C$ = maximum uptake and $T$ = effective half-life. The thyroid weight was calculated assuming that 1 ml (ultrasound volume) corresponds to 1 g tissue, with the ellipsoid formula: width (cm) × length (cm) × thickness (cm) × $\pi / 6$ for each lobe.

Effective half-life and maximum uptake were determined after application of a diagnostic activity of 27 mCi (1 MBq). Iodine kinetics were measured in all patients at 3, 6, 24 and 48 h. After application of the therapeutic activity, the iodine kinetics were measured again daily during 5 days and the radiation dose actually absorbed by the gland (Gy) was determined. $^{131}$I uptake in the neck was measured by a scintillation counter (Sopha Medical, Paris, France).

The follow-up was every 3 months during the first year, then every 6 months. The patients were classified as hyperthyroid (elevated concentration of $T_4$ and $T_3$), permanent hypothyroid (persistent decrease of $T_4$ and $T_3$) or euthyroid. Hypothyroid patients who were symptomatic received L-T$_3$ (liothyronine) in order to monitor the course of endogenous thyroid secretion (plasma FT$_4$).

**Statistics**

Statistical analysis was performed with the Statview 4.5 Statistical Software Program (Abacus Concepts, Calabasas, CA, USA). An ANOVA and the Scheffe test were used to compare the pretreatment variables. The relationship between administered dose and organ dose was assessed by simple regression. Data are reported as the mean ± S.D. $P$ values less than 0.05 were considered statistically significant.

**Results**

There was a significant relation between administered dose and organ dose (Fig. 1); the mean coefficient of variation for organ dose was 45% (36–232 Gy) (Table 1).
The pretreatment data are shown in Table 2. The age and the pretreatment values of FT₄, FT₃, 24 h iodine excretion, thyroid weight, organ dose and the number of patients with rTSHAb or TPOAb did not differ among the three groups. The maximum radioiodine uptake was higher in the group of patients who developed hyperthyroidism in comparison with patients who remained euthyroid (P < 0.05). Plasma rTSHAb and TPOAb were slightly higher in the group of patients who developed permanent hypothyroidism but the difference did not reach statistical significance. The outcome after ¹³¹I therapy of 100 patients (as none of them was lost to follow-up) and according to the final follow-up period is shown in Table 3. Twenty-six patients (26%) remained euthyroid after radioiodine therapy, while 33 (33%) remained or relapsed hyperthyroidism and 41 (41%) became permanent hypothyroid.

Discussion

Strictly speaking, the individualized dosimetry treatment of GD enabled euthyroidism in roughly a quarter of patients, and failed in 74% of patients, as hypothyroidism was not rated as a therapeutic success. Hyperthyroidism or permanent hypothyroidism occurred mainly during the first year, since hyperthyroidism was biochemically detected in 33 patients and early permanent hypothyroidism in 36 patients. The variability in the effectiveness of radioiodine in GD seems related to factors that determine the actual radiation effect of ¹³¹I: thyroid size, the effective halftime of ¹³¹I in the thyroid gland and the radioiodine uptake. Even if we could determine the unknowns useful for calculating the individual dose more precisely, the exact delivered thyroid dose, although correlated to the therapeutic dose, was highly variable and was not statistically different between the three groups. Furthermore the increasing organ dose with the administered dose may explain, at least in part, the absence of predictability of an ablative dose (10), or the equivalence between a semiquantitative approach and a calculated radioiodine dose (11).

We noticed, in line with others, a bimodal pattern of the incidence of hypothyroidism, with early and late occurrence. The higher number of patients with positive TPOAb in the hypothyroid group, although not significant, is in accord with the concept that two different mechanisms are involved in these phenomena. Early hypothyroidism seems related to the organ dose, whereas late hypothyroidism is probably related to an autoimmune process of GD (12, 13). Similarly the numbers of patients with positive rTSHAb were not different among the three groups in our study, although some previous results suggest that rTSHAb activity may cause a recovery of cell function following irradiation and is associated with a relative resistance.

![Figure 1](image)

**Figure 1** Relationship between administered dose and organ dose kinetics assessed by single regression (P < 0.003).

**Table 1** Coefficient of variation of organ dose according to the administered dose.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Coefficient of variation (%)</th>
<th>(range)</th>
</tr>
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<tbody>
<tr>
<td>≤ 2 mCi (n = 52)</td>
<td>33%</td>
<td>(40–150)</td>
</tr>
<tr>
<td>2 &lt; dose ≤ 3 mCi (n = 32)</td>
<td>45%</td>
<td>(36–223)</td>
</tr>
<tr>
<td>&gt; 3 mCi (n = 16)</td>
<td>57%</td>
<td>(44–232)</td>
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to radiiodine therapy (14). A plausible explanation may be that we did not have the opportunity to determine the amount of cAMP produced by rTSHAb on cultured cells and therefore to determine if these antibodies were stimulating or blocking.

As many other confusing factors may influence the results of radiiodine treatment, such as combined antithyroid drug regimen, uncontrolled iodine intake, patients with disseminated functional autonomy, or patients with recurrences after medical or surgical therapy (15), our study concerned only patients with a first GD episode, without antithyroid drug therapy, and with no excessive 24 h iodine excretion. An increased iodine intake could have explained radioresistance and radiiodine failure. On the other hand, iodine deficiency could induce functional autonomy. The coexistence of GD and Graves' disease might also reduce the radiosensitivity of Graves' thyroids (16). Even if it cannot be excluded in seven patients with low iodine excretion levels, diffuse uptake on radioisotope scintigraphy was required for inclusion and 24 h iodine excretion was not different among groups. The clinical outcome was still disappointing after individual dosimetry most probably because the individual target tissue sensitivity still remains unknown. A low dose, 50 Gy, is satisfactory for some authors (17), a target dose of 200 Gy is necessary to lead to a successful therapeutic outcome in about 80% of the patients for other authors, if hypothyroidism is considered as a therapeutic success (18). Finally it should be borne in mind that the latter report has shown that the relationship between the rate of eliminated hyperthyroidism and the radiation dose takes an exponential course, making the individual ideal dose difficult to achieve with a ratio.

In conclusion, these results raise doubt on the need for detailed study kinetics, at least at the present time, of both test and therapeutic doses to optimize results of radiiodine in treatment of GD. In our opinion, the simplistic ratios used for 50 years (9, 19) to calculate the individual target dose to deliver to the thyroid are not adapted, and the determination of factors other than the three generally taken into consideration, adds little for the prediction of failure or success. However, further research seems necessary in this field since neither a standard nor a calculated activity is entirely satisfactory for eliminating GD hyperthyroidism.

### References

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