Changing trends in the treatment of Graves' disease with radioiodine: a 12-year experience in a university hospital*

Mudanças evolutivas no tratamento da doença de Graves com iodo radioativo: 12 anos de experiência em um hospital universitário

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Abstract **OBJECTIVE: To evaluate the changes in clinical parameters and in the approach to patients submitted to radioiodine therapy for Graves' disease. MATERIALS AND METHODS: Dossiers of 226 patients submitted to radioiodine therapy for Graves' disease in the period between January 1990 and December 2001 were retrospectively evaluated. For the purposes of statistical analysis, the 12-year period was subdivided into three periods of 4 years, with a comparison of clinical and laboratory variables in these periods. RESULTS: The authors have observed that the total number of patients referred for radioiodine therapy as well as the percentage of female patients presented a significant increase (from 62% to 86%; $p = 0.005$). The percentage of patients pretreated with methimazole before radioiodine therapy increased significantly (from 9.1% to 35.6%; $p = 0.03$). The mean radioiodine dose delivered has also presented a significant increase (from 7.6 mCi to 12.7 mCi; $p = 0.000003$) with a direct reflection on a higher percentage of patients cured one year after the radioiodine therapy (from 55.6% to 83.7%; $p = 0.004$). CONCLUSION: Radioiodine therapy has increasingly been accepted for treatment of patients with Graves' disease and the doses delivered have increased to achieve a permanent cure as well as a reduction of the chances of recurrence.**

Keywords: Graves' disease; Methimazole; Sodium iodide – therapeutic use.

Resumo **OBJETIVO: Avaliar a mudança no perfil e abordagem dos pacientes com doença de Graves submetidos a dose terapêutica de radioiodo. MATERIAIS E MÉTODOS: Avaliamos, retrospectivamente, 226 pacientes portadores de doença de Graves submetidos a dose terapêutica de radioiodo entre janeiro de 1990 e dezembro de 2001. O período de 12 anos foi dividido em três períodos de 4 anos para fins de análise estatística, sendo comparadas variáveis clínicas e laboratoriais nos períodos descritos. RESULTADOS: Constatamos que o número de pacientes encaminhados para a dose terapêutica, assim como o percentual de pacientes do sexo feminino (de 62% para 86%; $p = 0,005$), tiveram incremento significativo. Houve aumento significativo no percentual de pacientes em uso de metimazol previamente à dose terapêutica (de 9,1% para 35,6%; $p = 0,03$). A dose média de iodo administrada também teve incremento significativo (de 7,6 mCi para 12,7 mCi; $p = 0,000003$), com reflexo direto em um maior percentual de pacientes curados (de 55,6% para 83,7%; $p = 0,004$) um ano pós-dose terapêutica. CONCLUSÃO: A dose terapêutica de radioiodo tem sido um método cada vez mais aceito nos pacientes com doença de Graves e a dose administrada tem sido cada vez maior, no intuito de cura permanente e diminuição das chances de recidiva.**

Unitermos: Doença de Graves; Metimazol; Iodeto de sódio – uso terapêutico.

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INTRODUCTION

More than 60 years have passed since the first description of radioactive iodine in the treatment of hyperthyroidism, in 1941 at the Massachusetts General Hospital in Boston, the isotope NaI-^{130}I being utilized at that time[1,2]. Because of the low cost, higher effectiveness in the thyroid cells destruction, and eight-day half-life, NaI-^{131}I has become the isotope of choice and is still widely utilized nowadays.

However, antithyroid drugs have been the first option for treating hyperthyroidism, particularly Graves' disease, not only in Brazil but also in the whole South America[3], principally aiming at achieving the disease remission. Considering the mean cost of treatment and the mean rate of remission after 12–24 months of treatment (approximately 50–60%)[4–9], the early indication for a definite treatment with NaI-^{131}I (therapeutic dose – TD) should be a more frequent option.

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Issues regarding the safety of NaI-^{131}I with emphasis on female patients and a possible effect of this isotope on their fertility have represented a hindrance to the early referral of patients for treatment.

Aiming at evaluating the possible changes in the profile of patients referred for TD, as well as the change in the conduct related to the administered dose and the consequential effect on the rate of cure of these patients, the authors collected data in the Unit of Nuclear Medicine of Hospital Universitário Clementino Fraga Filho – Universidade Federal do Rio de Janeiro (HUCFF-UFRJ), in a 12-year period between January 1990 and December 2001. The evaluation of the TD effectiveness as well as the influence of the change in the TD calculation was based on the analysis of the thyroid functional status one year after the TD.

MATERIALS AND METHODS

A retrospective study was developed with analysis of medical records of patients submitted to TD in the Unit of Nuclear Medicine of HUCFF-UFRJ, in the period from January 1990 to December 2001. The NaI-^{131}I doses calculation was based on the thyroid volume observed at clinical examination, the 24-hour NaI-^{131}I uptake, the hyperthyroidism severity and the eventual presence of comorbidities. Doses ranged from 50–150 μCi/g of thyroid tissue, but no report was found on the values of μCi/g thyroid tissue defined for each of the periods covered by the present study. Considering that the mentioned period is a continuous variable and, for the purposes of comparative analysis, the 12 years were segmented into four-year periods as follows: January 1990 to December 1993 (period 1), January 1994 to December 1997 (period 2), and January 1998 to December 2001 (period 3). The present study included patients submitted to TD, with decompensated hyperthyroidism (decreased TSH level and increased T4 level) in association with signs and symptoms of hyperthyroidism, with or without previous treatment with antithyroid drugs. Pre-TD laboratory test included the latest hormone dosage and therefore the hormone level reflecting the degree of hyperthyroidism decompensation in spite of antithyroid therapy. The sample uniformity was achieved through exclusion of patients based on the following criteria: patients submitted to thyroidectomy previously to the TD; patients previously submitted to TD; patients submitted to TD for multinodular toxic goiter or single toxic nodule undergoing antithyroid therapy for less than three months before TD; patients submitted to TD and undergoing antithyroid therapy; patients without any hormone dosage in the 9-12 month post-TD interval; patients with no pre-TD clinical and laboratory data.

The following variables were included for the purposes of statistical analysis: age, sex, time of antithyroid therapy, goiter volume, pre-TD 24-hour NaI-^{131}I uptake, pre-TD hormone levels, dose of NaI-^{131}I delivered, type of antithyroid drug, antithyroid drug dose, post-TD (9–12 months) hormone levels with classification of the functional thyroid status in this period (cured or non-cured).

Antithyroid drug dose corresponded to the dose received by the patient at the time of the pre-TD withdrawal. Only patients undergoing antithyroid therapy for at least three months could be included in the group with pre-TD antithyroid therapy. Patients without antithyroid drugs for more than three months were considered as without pre-TD antithyroid therapy. The goiter size was determined through clinical evaluation and graded from 0 to 3 as follows: 0 = absent goiter, 1 = one- to two-fold increased thyroid, 2 = more than two- to four-fold increased thyroid, and 3 = more than four-fold increased thyroid. Laboratory tests for hormone dosage included free T4 (ng/dl), TSH (mU/l), total T4 (μg/dl) and total T3 (ng/dl). In the post-TD 9-12-month period the patients were re-evaluated for hormone dosage and classified into two different groups as follows:

a) Cured patients: with normal free T4 levels (euthyroid patients); with normal free T4 levels using levothyroxine (treated hyperthyroid patients); low free T4 levels with or without levothyroxine (hypothyroid or compensated patients).

b) Non-cured patients: with high free T4 levels without any medication; with high free T4 levels using antithyroid drugs; normal free T4 levels under antithyroid therapy.

Patients with high free T4 levels under levothyroxine therapy as well as those with low free T4 levels under antithyroid therapy were classified according to their progression along the follow-up. TSH serum levels were not taken into consideration for this classification because the thyroid axis suppression may extend for a long period even after the clinical euthyroid status is achieved[10,11].

In patients whose free T4 level was not available, the total T4 level was considered according to the same, above mentioned criteria.

Statistical analysis

The software Epi-Info version 6.0 was utilized for statistical analysis. The Kruskal-Wallis test was utilized for comparison of numerical and category variables among age, time of antithyroid therapy, free T4 levels, total T4 levels, total T3 levels, NaI-^{131}I uptake and therapeutic dose in the three periods determined for the present study. The chi-square (χ^2) test was utilized for bivariate analysis with comparison of two category variables among sex, goiter volume (segmented from 0 to 4), type of antithyroid drug utilized and hyperthyroidism remission or not one year after TD in the three mentioned periods, with values > 3.84 corresponding to $p < 0.05$. Statistical significance was determined at 5% or $p < 0,05$.

RESULTS

Among 774 dossiers of patients with hyperthyroidism submitted to TD, 226 which met both the mentioned inclusion and exclusion criteria were analyzed. All the results are shown on Table 1. Over the years, a significant increase was observed in the number of patients referred for TD (27, 70 and 129 in the first, was similar over the years and third periods, respectively). Over the years, the clinical profile of the patients referred for TD remained stable as reflected by the statistical similarity of data regarding goiter volume, hormone levels (free T4, total T3 and TSH) pre-TD iodine uptake as well as the pre-TD antithyroid drug dose. Statistically significant changes in relation to the clinical profile of the patients are reflected by the following aspects: 1) a significant increase in the num-

Table 1 Characteristics according to period in years

	January/1990–December/1993	January/1994–December/1997	January/1998–December/2001	*p*-value
Number of patients	27	70	129	
Sex (female/male)	17/10	58/12	112/17	0.005
Age	46.4 (± 12.5)	44.0 (± 11.2)	42.9 (± 12.0)	0.070
Goiter				0.621
0	1 (3.7%)	8 (11.3%)	7 (5.4%)	
1	14 (51.9%)	37 (52.9%)	67 (51.9%)	
2	12 (44.4%)	23 (32.9%)	51 (39.5%)	
3	0 (0%)	2 (2.9%)	4 (3.1%)	
Dose	7.6 (± 1.5)	9.4 (± 2.5)	12.7 (± 3.6)	0.000003
24 hours captation	69.6 (± 18.9)	63.5 (± 19.6)	61.9 (± 17.0)	0.132
Antithyroid therapy (months)	14.9 (± 12.7)	13.4 (± 11.2)	11.6 (± 10.5)	0.289
Free T4	4.4 (± 2.2)	4.0 (± 2.1)	3.6 (± 1.7)	0.228
Total T3	353.5 (± 165)	336.7 (± 196)	324.6 (± 202)	0.558
Total T4	18.8 (± 8.0)	18.2 (± 6.7)	18.9 (± 6.7)	0.757
Antithyroid drug				0.030
Propylthiouracil	20 (90.9%)	36 (76.6%)	67 (64.4%)	
Methimazole	2 (9.1%)	11 (23.4%)	37 (35.6%)	
12 months after TD				0.004
Cured patients	15 (55.6%)	52 (74.3%)	108 (83.7%)	
Non-cured patients	12 (44.4%)	18 (25.7%)	21 (16.3%)	

ber of female patients referred for TD, particularly as from 1993 (62.9%, 82.8% and 86.8% respectively in the first, second and third periods, corresponding to $p = 0.005$); 2) type of pre-TD antithyroid therapy, with a significant increase in the number of patients utilizing methimazole (9.1%, 23.4% and 35.6% respectively in the first, second and third period, with $p = 0.03$), as demonstrated on Figure 1.

The radioiodine dose delivered presented a quite significant increase (7.6, 9.4 and 12.7 mCi, respectively in the first, second and third periods, with $p = 0.000003$), as shown on Figure 2, affecting directly the percentage of patients cured of hyperthyroidism one year after the TD (55.6%, 74.3% and 83.7%, respectively in the first, second and third periods, with $p = 0.004$) (Figure 3).

In a separate analysis of patients cured one year after the DT, no significant change in the percentage of hyperthyroid patients was observed with 9/15 (60%), 36/52 (69%) and 67/108 (62%) respectively in the first, second and third periods.

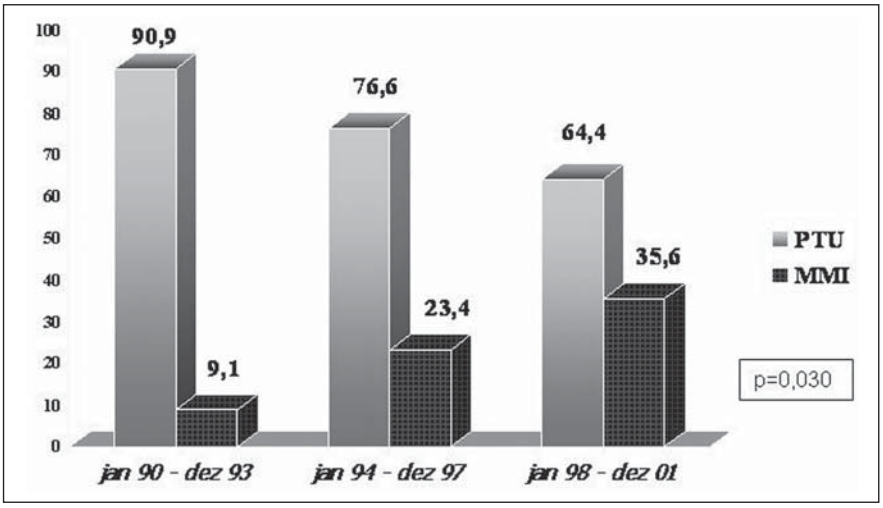

Figure 1. Percentage of antithyroid drugs utilized previously to the therapeutic radioiodine dose.

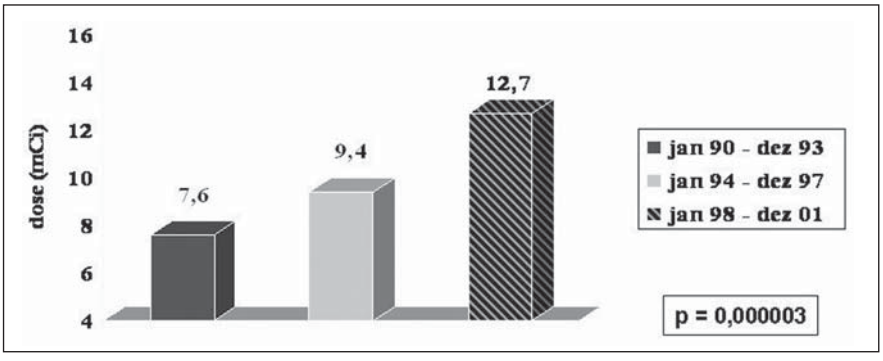

Figure 2. Mean dose of radioactive iodine (mCi) delivered over each four-year period.

DISCUSSION

The ideal therapy for hyperthyroidism is still to be established, and the three clas-

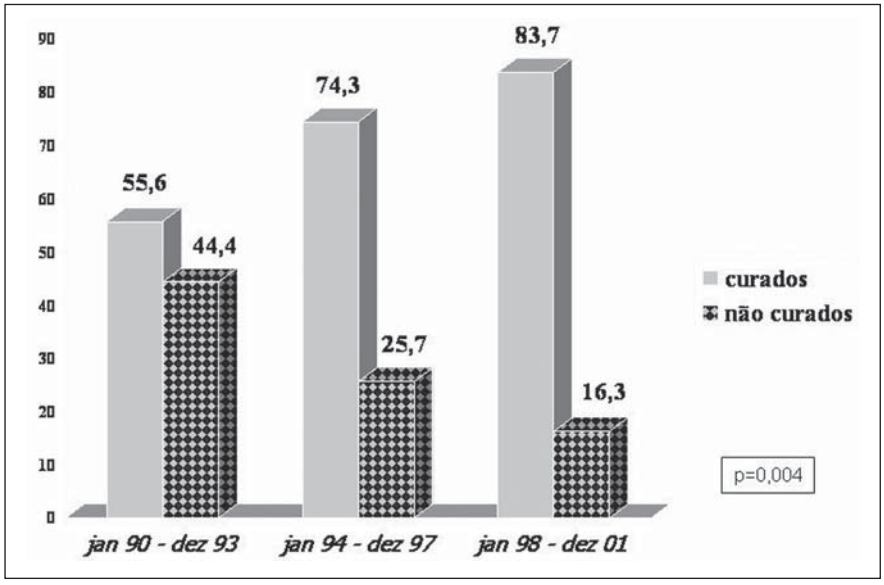

Figure 3. Percentage of cured patients one year after the therapeutic dose of radioactive iodine per four-year period.

sical therapeutic approaches - namely, surgery, antithyroid therapy or TD of NaI-^{131}I - present both advantages and disadvantages[12–15]. The criteria for administration of radioactive iodine as a treatment for hyperthyroidism in Graves' disease still lack uniformity through different countries, especially in relation to the administered dose, moment of administration and which factors might affect the treatment effectiveness. In the USA, there is a remarkable preference for TD, with early indication of this type of therapy[16]. According to scientific citations, the dose per gram of thyroid tissue has been progressively increased in order to prevent recidivation or even minimizing chances of non-remission with necessity of repetition of the TD[17].

In the present study the authors observed that the number of patients referred for TD more than duplicated at each period, reflecting its higher acceptance as an excellent method for definite treatment, besides the therapy safety[12,17]. The influence of the North American literature, which reports the indication of radioactive iodine in up to 69% of cases of hyperthyroidism as the initial method of treatment[16], may also be an associated factor.

As regards the mean pre-TD antithyroid therapy time, there was a subtle decrease over the years, although without any significant difference ($p = 0.289$), maybe suggesting a trend to an earlier indication for a definite therapy. As regards the utilization of pre-TD antithyroid therapy, there was a significant increase in the number o patients treated with methimazole (Figure 1), maybe reflecting the results of some studies suggesting a more pronounced radioprotector effect of propylthiouracil[18–22], besides the major facility for a pre-TD methimazole withdrawal[23].

Another interesting finding was the increase in the percentage of female patients referred for TD, with a 60.7% female prevalence in the period between 1990 and 1993, increasing to 83% in the 1994–1997 period and remaining stable (86.3%) in the 1998–2001 period. These data reflect not only the TD safety, especially for young patients with Graves' disease, as demonstrated by Metso et al. in a recent population study with 2,793 patients[24], but re-emphasizing the radioactive iodine safety even for women in childbearing age, as already demonstrated by Brandão et al.[25], considering that, among the 189 women included in the study, 40.7% ($n = 77$) were 16–40-year old, and 26.7% ($n = 30$) were 16–30 year old.

A crucial issue to be discussed is the difference in the radioiodine doses (increase from 7.6 mCi to 9.4 mCi and 12.7 mCi, with $p = 0.000003$). Much has been tried to define an ideal dose[17,26], from low, fixed doses[27,28] and dose calculations[12] to achieve euthyroidism, to high fixed doses[29,30], aiming at guaranteeing the hypothyroidism and, consequently, the "cure" of hyperthyroidism. It is clearly demonstrated that the higher the dose, the higher the rate of hypothyroidism; and the lower the dose, the higher the chance of recidivation. Dose calculations, where utilized, are extremely variable (75–200 μCi/g)[12,17], even at a same health center, especially in relation to goiter volume, hyperthyroidism severity and presence of cardiopathy. The utilization of ultrasonography in the measurement of goiter volume is of little practical significance and does not make any difference in the final effect of TD as compared with the clinical evaluation[31]. Although it is seemingly non-practical, a simple methodology was recently described for biokinetic evaluation of radioactive iodine as well as the evaluation of the absorbed dose/administered activity ratio[32], that might be useful for more effective dose calculations. However, this methodology has not been routinely adopted yet. So, the currently adopted doses have been increasingly higher, particularly when the eventual presence of comorbidities and possible risks for patients (cardiopathy being the most feared one) are taken into consideration. Upon all these considerations, one can clearly observe the increase in calculated doses over the years aiming at guaranteeing a cure of hyperthyroidism as fast as possible, even at the expense of a relatively early onset of hypothyroidism. Patients with not so severe hyperthyroidism, without comorbidities and with good indicators for post antithyroid therapy remission cannot be forgotten[5,33], to give them a chance of euthyroid independently from the utilization of any medication. So, it seems to be reasonable to observe all the indicators of Graves' disease severity and discussing with her/him the best option for treatment.

Finally, as well as Hernández-Jiménez et al.[34], we could observe that the linear increase in the administered dose (Figure 2) corresponded to a progressive increase in the percentage of cured patients (Figure 3) — from 55% in the first period, to 74% in the second and, finally 83% in the third period ($p = 0.004$).

The authors concluded that in their health unit, the number of patients referred

for TD presented a quite significant increase, which corroborates the endocrinologists' acceptance of radioactive iodine as a safe method for definite treatment for Graves' disease. The administered radioiodine dose presented a significant increase in over the three periods covered by the present study coincidentally with a significant decrease in the percentage of non-cured patients one year after the TD.

Additionally, it may be concluded that the patients have not been referred earlier for TD, and that the utilization of methimazole has increased in patients who are to be submitted to radioiodine therapy, maybe because of the very probable propylthiouracil radioprotector effect already confirmed by prospective controlled studies[20,21].

Finally, a significant percent increase was observed in the female group (even women in childbearing age) referred for TD, approaching the actual female prevalence of Graves' disease.

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