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English Section

Editorial  Nucleology, nuclear medicine, molecular nuclear medicine and subspecialties. P. Grammaticos

Review Articles  PET imaging in cardiology. G. Chacko

Feline hyperthyroidism. The contribution of nuclear medicine. P. Lass, S. Kaniuka

Original Article
Cold infarction areas of varying size in the presence of left ventricular dysfunction: the impact on left ventricular ejection fraction determination by gated SPECT compared to radionuclide ventriculography. F. Canbaz, T. Basoglu, S. U. Semirgin, O. Yapiçi, M. Yazıcı

Research Articles
Diuretic radionuclide renography in assessing Anderson-Hynes pyeloplasty in unilateral pelviureteric junction obstruction. M. Tripatthi, R. Kumar, N. Chandrashekar, S. Sharma, C. Bal, G. Bandopadhyaya, A. Malhotra

Comparative evaluation of two fixed doses of 185 and 370 MBq 131I, for the treatment of Graves’ disease resistant to antithyroid drugs. A. F. Esfahani, V. R. D. Kakkhi, B. Fallahi, M. Eftekhar, D. Beiki, M. Saghari

The role of 99mTc(V)-DMSA scan as compared to 99mTc-MDP and CT scans in imaging the primary tumor and metastases of osteosarcoma antithyroid drugs. A. Zissimopoulos, A. Zanglis, D. Andreopoulou, N. Baziatis


Case Reports
Unilateral absent lung ventilation and perfusion due to a hilar mass. A. Ghilanrezanezhad, M. Eftekhar, A. F. Esfahani, B. F. Sichani, D. Beiki

Osteoid osteoma mimicking chronic arthritis. Diagnosis by bone scintigraphy. G. Kolliasos, N. Katsiki

International Meeting
Original and important results from an International Meeting held in Thessaloniki, Macedonia, Greece

Correspondence Pelvic vascular tumours in 3-phase bone scintigraphy - The future of diagnostic imaging: not exclusively or maybe not in nuclear medicine - Reply: Opportunities and challenges in the nuclear medicine arena

Forthcoming Meetings, Instructions to Authors

Greek Section – Abstracts in English

Editorial Note  Conclusions from a national Congress of Nuclear Medicine. The address of chairman of Congress. Our speciality as "Nucleology"

Editorial  Stereotactic radiosurgery in neuro surgery. H. Kourtopoulos

Short review

Original Article
Right and left ventricular ejection fraction evaluation in patients with chronic pulmonary disease. Comparison of nuclear medicine methods. I. Iakovou, N. Karatzas, D. Oikonomidis, A. Psarakou

Abstracts from the English Section

Instructions to Authors

Authors’ and Subject Index of Volume 8, 2005
Comparative evaluation of two fixed doses of 185 and 370 MBq $^{131}$I, for the treatment of Graves’ disease resistant to antithyroid drugs

Abstract

Radioiodine ($^{131}$I) treatment is often applied for the treatment of Graves’ disease (GD). The optimal dose of $^{131}$I for Graves’ hyperthyroidism is debated. Various techniques suggest either fixed doses or varying doses based on elaborate calculations of the gland size, $^{131}$I uptake, and $^{131}$I turnover. Fixed dose regimens avoid dose calculations but there is no consensus on the actual dose to be administered. We compared two routinely recommended fixed $^{131}$I doses of 185 and 370 MBq for this purpose. Fifty nine patients with GD who had not been previously treated with $^{131}$I were randomized in two groups. Group A consisted of 33 patients who were treated with 185 MBq of $^{131}$I. Group B consisted of 26 patients who were treated with 370 MBq of $^{131}$I. Group A patients were 21% male and 78% female, mean age 38.1±14.4, range 15 to 77 y. Group B patients were 27% male and 73% female, mean age 40.7±11.7, range 27 to 72 y. All patients were reexamined every six months for two years. The following clinical outcomes were noticed: a) Persistent hyperthyroidism, which was considered as failure to treatment, requiring further $^{131}$I treatment; b) Hypothyroidism; c) Hypothyroidism; d) Euthyroid state. Euthyroid and hypothyroid states were considered as a response to treatment of hyperthyroidism. In Group A, 10 patients (30.3%) became euthyroid and 6 (18.2%) hypothyroid (an overall response of 48.5%), while 17 (51.5%) remained hyperthyroid by the end of the follow-up period. In Group B, 10 patients (38%) became euthyroid and 13 (50%) hypothyroid, an overall response of 88.5%. No responders were 3 patients (11.5%). No correlation was noted between the outcome of treatment and age, sex, size of the thyroid gland or thyroid uptake in each Group of patients, while a significant correlation was noted between the disease outcome and the amount of administered $^{131}$I (P<0.003). The incidence of hypothyroidism by the end of two years of follow up was less in Group A than in Group B and the incidence of non-responders to treatment was lower in Group A. In view of the higher cost of treatment, the longer time elapsing to treatment, the number of office visits by the patients and the higher number of patients with persistent hyperthyroidism in Group A, we conclude that a fixed dose of $^{131}$I of 370 MBq is more useful and effective for the treatment of GD as compared to 185 MBq of $^{131}$I.


Introduction

Graves’ disease (GD) is the most common cause of hyperthyroidism, about 90% of all cases [1]. Many authors consider radioiodine ($^{131}$I) as the treatment of choice for GD compared to antithyroid medications or surgery [2,3]. Fixed $^{131}$I doses or doses calculated by complex formulas depending on the thyroid mass, the radiation absorbed dose etc have been proposed for the treatment of GD, but both therapeutic schedules are not totally effective [4]. There is no general consensus over the appropriate dose of $^{131}$I for the treatment of GD. Doses varying from 100 to 1090 MBq have been suggested [2]. This may be due to different tissue radiosensitivity and different radiation absorbed dose. Radiation absorbed dose depends not only on the amount of ingested iodine, but also on factors such as thyroid uptake and effective half-life of iodine in the thyroid gland and the mass of the thyroid gland [2]. It may also be due to antibodies stimulating, blocking or destroying thyroid tissue [5].

Complex formulas used for calculating the amount of $^{131}$I are based on the weight, the size of the thyroid gland, radioactive iodine uptake (RAIU), and the amount of $^{131}$I retained in the gland [2,4,6] and measurement of each of these factors may be inaccurate. Nowadays, fixed dose protocols are preferable [7,8]. Since higher $^{131}$I doses increase the rate of early hypothyroidism and conversely, lower $^{131}$I doses increase the rate of non responders [1,2,9], the need for trying to estimate a comparatively better dose of $^{131}$I for the treatment of GD is obvious. We have thus compared the effect of a low and a high fixed dose of $^{131}$I in two Groups of patients with GD.
Patients and methods

Fifty-nine patients with typical clinical and laboratory findings characteristic of GD were studied [2,4]. They all had increased 131I uptake, and diffuse goiter. These patients were repeatedly resistant to antithyroid drug treatment and referred to our institute for treatment with 131I. Patients were studied prospectively in a randomized clinical trial approved by the ethics committee of Tehran University of Medical Sciences after we had received their informed consent. Patients with a history of other thyroid diseases, other serious clinical illnesses, previous surgical treatment of the thyroid gland or treatment with 131I, women who were pregnant or nursing and the subjects who failed to attend even one of the four scheduled follow-up sessions, were excluded from the study. For those patients receiving antithyroid medication to control hyperthyroid hypermetabolic state prior to 131I treatment, their medication was discontinued for at least 72 h before the RAII measurement [2,4]. Afterwards, patients were randomly allocated in two fixed dose groups. Group A consisted of patients who received a low fixed dose of 185 MBq and Group B of patients who received a high fixed dose of 370 MBq of 131I, administered orally in liquid form. Every six months for two years after the intake of 131I, all patients were reexamined by two specialist physicians and had also thyroid function tests: free thyroxine (FT4), free triiodothyronine (FT3) and thyroid stimulating hormone (TSH). The size of the thyroid gland was described as normal (thyroid neither palpable nor visible), mild diffuse goiter (thyroid palpable but not visible), moderate diffuse goiter (thyroid palpable and visible at a distance of less than 1 m) and severe diffuse or huge goiter (thyroid was palpable and visible from a distance of more than 1 m). To compare the recurrence and response rates between these Groups, the Chi square test was used. Binary logistic regression analysis was also used to determine statistical correlation of studied variables and treatment response. Values of the statistical criterion of P of less than 0.05 were considered statistically significant.

Results

As shown in Table 1, there was no statistical difference between Groups A and B as to the age, gender, the size of the thyroid gland and RAIIU. As shown in Table 2, two years after treatment significant difference in thyroid functional status between the two groups was noted (Chi-square test, P=0.003).

After the two-year follow-up period, from the 33 patients of Group A, 16 (48.5%) became euthyroid or hypothyroid, so the overall rate of favorable treatment in Group A was 48.5%, while in Group B it was 88.5% (23/26) (P<0.001).

By using a co-variate analysis, stepwise logistic regression, the dose of the ingested 131I was the only variable which had a significant correlation with patients’ clinical response to treatment after the two-year follow-up period (in cases that received 185 MBq of 131I, the likelihood of a favorable outcome was 63% higher compared to cases that received 370 MBq of 131I).

Table 1. Comparison of the two groups of patients based on the variables: age, gender, size of the thyroid and uptake of 131I%

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>38.15±14.42</td>
<td>40.69±11.75</td>
<td>0.47</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>21.2%</td>
<td>26.9%</td>
</tr>
<tr>
<td>Female</td>
<td>78.8%</td>
<td>73.1%</td>
<td>73.1%</td>
</tr>
<tr>
<td>N(1) or Mild DG(2)</td>
<td>54.5%</td>
<td>34.6%</td>
<td>0.173</td>
</tr>
<tr>
<td>Size of thyroid</td>
<td>Moderate DG</td>
<td>42.4%</td>
<td>65.4%</td>
</tr>
<tr>
<td>Severe DG</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Thyroid uptake % (mean±SD)</td>
<td>59.85±19.74</td>
<td>59.41±17.54</td>
<td>0.930</td>
</tr>
</tbody>
</table>

(1) Standard deviation, (2) Normal, (3) Diffuse goiter

Table 2. Thyroid state two years after treatment in Groups A and B

<table>
<thead>
<tr>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
<th>Euthyroidism</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 (51.5%)</td>
<td>6 (18.2%)</td>
<td>10 (30.3%)</td>
<td>Group A</td>
</tr>
<tr>
<td>3 (11.5%)</td>
<td>13 (50%)</td>
<td>10 (38.5%)</td>
<td>Group B</td>
</tr>
<tr>
<td>20</td>
<td>19</td>
<td>20</td>
<td>Total</td>
</tr>
<tr>
<td>P=0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Comparison of the thyroid state after two years with gender, thyroid size, age and thyroid uptake in all 59 patients studied

<table>
<thead>
<tr>
<th>Total Number</th>
<th>Thyroid state after two years follow-up</th>
<th>Variable</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperthyroid</td>
<td>Hypothyroid</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>14 (100%)</td>
<td>5 (35.71%)</td>
<td>4 (26.57%)</td>
<td>5 (35.71%)</td>
</tr>
<tr>
<td>45 (100%)</td>
<td>15 (33.33%)</td>
<td>15 (33.33%)</td>
<td>15 (33.33%)</td>
</tr>
<tr>
<td>27 (100%)</td>
<td>10 (37.03%)</td>
<td>8 (29.62%)</td>
<td>9 (33.33%)</td>
</tr>
<tr>
<td>31 (100%)</td>
<td>9 (29.03%)</td>
<td>11 (35.48%)</td>
<td>11 (35.48%)</td>
</tr>
<tr>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>15 (100%)</td>
<td>5 (33.33%)</td>
<td>6 (40%)</td>
<td>4 (26.66%)</td>
</tr>
<tr>
<td>36 (100%)</td>
<td>11 (30.55%)</td>
<td>12 (33.3%)</td>
<td>13 (36.11%)</td>
</tr>
<tr>
<td>8 (100%)</td>
<td>4 (50%)</td>
<td>1 (12.5%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>10 (100%)</td>
<td>5 (50%)</td>
<td>2 (20%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>18 (100%)</td>
<td>5 (27.77%)</td>
<td>5 (27.77%)</td>
<td>8 (44.44%)</td>
</tr>
<tr>
<td>31 (100%)</td>
<td>10 (32.25%)</td>
<td>12 (38.7%)</td>
<td>9 (29.03%)</td>
</tr>
</tbody>
</table>

(1) Normal, (2) Diffuse goiter
lapsed or were favorably treated). (P=0.001). The other variables (age, sex, thyroid size and RAIU) showed no correlation with the outcome of treatment in every Group (Table 3).

Discussion

The ideal goal of the 131I treatment would be to induce euthyroidism although hypothyroidism may be transient and return to euthyroidism [4,7,8]. Survival analysis by others has not demonstrated any difference between the fixed and the adjusted dose methods [9]. A standard dose of 2.03–2.96 MBq/g of estimated thyroid tissue was reported to provide the best outcome in terms of inducing euthyroidism and early hypothyroidism [2,10]. It has been reported that the use of a fixed dose method simplifies treatment and also has a potential cost saving [9]. Most cases of hypothyroidism occur during the first two years of treatment [1,11]. The incidence of hypothyroidism during these two years in our study for Groups A and B was 18.2% and 50% respectively. Others found with the adjusted dosimetric method an one-year incidence of hypothyroidism of 7%-25% [4].

After the first two years of treatment with 131I, hypothyroidism occurs at a rate of 2%-3% per year [2]. Low-dose regimens will reduce the incidence of hypothyroidism in the first year, but after 15 years the incidence of delayed hypothyroidism will be considerable (35%-40%). High dose regimens will induce an even higher incidence of hypothyroidism (50%-70%) after 15 years [4]. Our results have shown a low incidence of hypothyroidism in Group A and a high incidence in Group B, 18% and 50% respectively. In a study by Allahabadia et al. (2001), patients with GD one year after given a single dose of 370 MBq had a higher rate of favorable treatment than those given 185 MBq, 84.6% vs. 66.6% respectively (P=0.0001). The incidence of hypothyroidism was 60.8% vs. 41.3%, respectively (P<0.0001) [12]. In another study, the rate of hypothyroidism one year after a fixed therapeutic dose of 369 MBq in GD was 61% [13], much greater than in our study (50%). This may be attributed to radiosensitivity, the size of the thyroid gland, radioactive iodine uptake (RAIU), and the amount of 131I retained by the gland [2,4,6].

Recurrence rate will change in accordance with the prescribed 131I dose. In our study, 51.5% of Group A and 11.5% of Group B patients had experienced recurrence of hyperthyroidism.

In a study of 605 patients with GD treated with 3 to 370 MBq of 131I, the overall response rate (euthyroid state or hypothyroidism) was 76.2%. No increase in the response rate was reported between doses of 3 to 185 MBq, but as the dose increased from the 185 MBq to 370 MBq the response rate increased from 70% to 87%. The recurrence rate that needed further treatment was 30% in the 185 MBq Group and 13% in the 370 MBq Group [14]. Our results have shown 48.5% response rate in Group A which is much lower than that reported in the above mentioned study. This may be due to variability in the studied population. However, the response rate for Group B was 88.5% which is similar with that of the above mentioned study.

Treatment costs must also be considered. According to our results, after a dose of 185 MBq of 131I, re-treatment is needed in 51.5% of the cases, whereas after 370 MBq only in 11.5% of the cases. If the first dose fails, the time for the completion of treatment after the second dose will increase the number of visits to the clinic, and there may be complications of the untreated cases of hyperthyroidism. Laboratory tests and re-treatment with a second 131I dose will also increase the overall cost of treatment as compared to the 370 MBq regimen. If we also consider the cost of disability and the reduced income of many patients, then treatment with doses of 370 MBq of 131I as compared to 185 MBq, appear to be more advantageous.

Age, sex, amount of iodine uptake, and thyroid size had no effect on the results of treatment in our study. Gilbert and Nordlyke (1988) also showed no correlation between age, sex, RAIU and response rate and also between thyroid weight and response rate except for the very large or the very small goiters [13]. Others have also found that gender and size of the thyroid gland were significantly independent prognostic factors for the therapeutic response after single doses of 131I, either 185 or 370 MBq were administered [12]. In the present study we had only one case with a very large goiter.

Based on our results it seemed that age, sex, iodine uptake, and even thyroid size have no role in the selection of the appropriate therapeutic dose of 131I for GD. High doses give better response to treatment and lower risk of recurrence, thus are preferable to the low dose radiiodine therapy.

Some of the researchers recommend for the treatment of GD even higher doses of 131I (555 MBq in one study). This high dose would ablate the thyroid and reduce subsequent recurrences [15,16]. However, even these high doses failed to treat all patients. Kendall Taylor et al [16] using 555 MBq of 131I found that 5.6% of the patients showed no therapeutic response. No increase in thyroid cancer, other malignant diseases, or adverse genetic effects had been reported [1,2,15].

In conclusion, a single fixed dose of 370 MBq 131I is highly effective in the treatment of GD and should be preferred over the 185 MBq dose because it gives a better response rate and is cost-effective.

Bibliography

## Instructions to authors

The full text of some papers is in Greek

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Comparative evaluation of two fixed doses of 185 and 370 MBq $^{131}$I, for the treatment of Graves’ disease resistant to antithyroid drugs

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Abstract
Radioiodine ($^{131}$I) treatment is often applied for the treatment of Graves’ disease (GD). The optimal dose of $^{131}$I for Graves’ hyperthyroidism is debated. Various techniques suggest either fixed doses or varying doses based on elaborate calculations of the gland size, $^{131}$I uptake, and $^{131}$I turnover. Fixed dose regimens avoid dose calculations but there is no consensus on the actual dose to be administered. We compared two routinely recommended fixed $^{131}$I doses of 185 and 370 MBq for this purpose. Fifty nine patients with GD who had not been previously treated with $^{131}$I were randomized in two groups. Group A consisted of 33 patients who were treated with 185 MBq of $^{131}$I. Group B consisted of 26 patients who were treated with 370 MBq of $^{131}$I. Group A patients were 21% male and 78% female, mean age 38.1±14.4, range 15 to 77 y. Group B patients were 27% male and 73% female, mean age 40.7 ±11.7, range 27 to 72 y. All patients were reexamined every six months for two years. The following clinical outcomes were noticed: a) Persistent hyperthyroidism, which was considered as failure to treatment, requiring further $^{131}$I treatment. b) Hypothyroidism; requiring life-long replacement treatment. c) Euthyroid state. Euthyroid and hypothyroid states were considered as a response to treatment of hyperthyroidism. In Group A, 10 patients (30.3%) became euthyroid and 6 (18.2%) hypothyroid (an overall response of 48.5%), while 17 (51.5%) remained hyperthyroid by the end of the follow-up period. In Group B, 10 patients (38%) became euthyroid and 13 (50%) hypothyroid, an overall response of 88.5%. Non responders were 3 patients (11.5%). No correlation was noted between the outcome of treatment and age, sex, size of the thyroid gland or thyroid uptake in each Group of patients, while a significant correlation was noted between the disease outcome and the amount of administered $^{131}$I (P<0.003). The incidence of hypothyroidism by the end of two years of follow up was less in Group A than in Group B and the incidence of non responders to treatment was lower in Group A. In view of the higher cost of treatment, the longer time elapsing to treatment, the number of office visits by the patients and the higher number of patients with persistent hyperthyroidism in Group A, we
conclude that a fixed dose of $^{131}$I of 370 MBq is more useful and effective for the treatment of GD as compared to 185 MBq of $^{131}$I.

Keywords: Graves’ disease – $^{131}$I treatment – Fixed $^{131}$I dose – Low $^{131}$I dose – High $^{131}$I dose – $^{131}$I dose evaluation

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