Radioiodine therapy in benign thyroid disorders. Evaluation of French nuclear medicine practices

Traitement des hyperthyroïdies par l’iode 131. Bilan des pratiques de prescription françaises

Delphine Bernard a,∗, Marie Dominique Desruet a, Marianne Wolf b, c, Julie Roux c, Camille Boin a, Roseline Mazet a, Céline Gallazzini c, Alex Calizzano c, Jean-Philippe Vuillez c, Benoît Allenet a, Daniel Fagret c

a Department of pharmacy, university hospital A. Michallon, CS 10217, 38043 Grenoble, France
b Department of endocrinology, CS 10217, 38043 Grenoble, France
c Department of nuclear medicine, CS 10217, 38043 Grenoble, France

Abstract

Objectives. – Radioiodine is currently used routinely in the treatment of hyperthyroidism including Graves’ disease (GD), toxic multinodular goitre (TMNG) and toxic solitary nodule (TSN) but no consensus exists on the most appropriate way to prescribe iodine – fixed dose or calculated doses based on the gland size or turnover of 131I. We carried out the first nationwide French survey assessing the current practices in radioiodine treatment of hyperthyroidism. Material and methods. – A questionnaire was sent to French nuclear medicine hospital units and cancer treatment centres (n = 69) about their practices in 2012. Results. – Euthyroidism was considered the successful outcome for 33% of respondents, whereas hypothyroidism was the aim in 26% of cases. Fixed activities were the commonest therapeutic approach (60.0% of GD prescribed doses and 72.5% for TMNG and TSN), followed by calculated activities from Marinelli’s formula (based on a single uptake value and thyroid volume). The fixed administered dose was chosen from between 1 to 3 levels of standard doses, depending on the patient characteristics. Factors influencing this choice were disease, with a median of 370 MBq for GD and 555 MBq for TSN and TMNG, thyroid volume (59%) and uptake (52%) with 131I or 99mTc. Even physicians using fixed doses performed pretherapeutic thyroid scan (98%). Conclusion. – This study shows that practices concerning the prescription of 131I therapeutic doses are heterogeneous. But the current trend in France, as in Europe, is the administration of fixed doses. The study provides the baseline data for exploring the evolution of French clinical practices.
© 2014 Published by Elsevier Masson SAS.

Keywords: Thyroid; Hyperthyroidism; Radioiodine dose; Graves’ disease

Résumé

Objectifs. – L’iode radioactif est utilisé en routine dans le traitement de l’hyperthyroïdie, comprenant la maladie de Basedow (Graves’ disease (GD)), le goitre multinodulaire toxique (GMNT) et le nodule solitaire toxique (NST), mais il n’existe aucun consensus sur la meilleure façon de prescrire de l’iode – dose fixe ou dose calculée sur la base de la taille de la glande ou du turnover de l’iode 131. Nous avons réalisé la première enquête nationale française évaluant les pratiques actuelles en matière de traitement à l’iode radioactif de l’hyperthyroïdie. Matériel et méthodes. – Un questionnaire a été envoyé en 2012 aux services hospitaliers français de médecine nucléaire ainsi qu’aux centres de traitement du cancer (n = 69) sur leurs pratiques. Résultats. – Une euthyroidie était considéré comme un succès pour 33 % des répondants, tandis qu’une hypothyroidie était le but dans 26 % des cas. Fixer l’activité thyroïdienne était l’approche thérapeutique la plus courante (60,0 % des doses prescrites pour GD et 72,5 % pour GMNT et NST), suivie par un calcul d’activité à partir de la formule de Marinelli (fondé sur une valeur d’absorption unique et sur le volume de la thyroïde). La dose fixe administrée a été choisie parmi 1 à 3 niveaux de doses standard, en fonction des caractéristiques du patient. Les facteurs influençant ce choix étaient la maladie, avec une médiane de 370 MBq pour la GD et de 555 MBq pour la NST et la GMNT, le volume de la thyroïde (59 %) et l’absorption (52 %) avec 131I ou 99mTc. Même les médecins utilisant des doses fixes effectuaient une scintigraphie

∗ Corresponding author.
E-mail address: dbernard@chu-grenoble.fr (D. Bernard).

http://dx.doi.org/10.1016/j.ando.2014.07.863
0003-4266© 2014 Published by Elsevier Masson SAS.
thyroidienne pré-thérapeutique (98 %). Conclusion. – Cette étude montre que les pratiques concernant la prescription de doses thérapeutiques $^{131}$I sont hétérogènes. Mais la tendance actuelle, en France comme en Europe, est l’administration de doses fixes. Cette étude fournit les données de base pour explorer l’évolution des pratiques cliniques françaises.

© 2014 Publié par Elsevier Masson SAS.

Mots clés : Thyroïde ; Hyperthyroïdie ; Iode 131 ; Maladie de Basedow

1. Introduction

Radioiodine ($^{131}$I) is used routinely in the treatment of various forms of hyperthyroidism including Graves’ disease (GD), toxic solitary nodule (TSN) and toxic multinodular goitre (TMNG). In France as in Europe, the aim of radioiodine therapy in hyperthyroidism is mainly to restore euthyroidism [1]. In this context, many studies attempted to identify the best method to determine the radioiodine activity, one that minimizes the risk of developing hypothyroidism while maximizing the cure rate of hyperthyroidism. The optimal value of doses is, however, still under discussion.

We reviewed the recommendations set out in papers published by the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) [2] in 2011, the European Association of Nuclear Medicine (EANM) [3] in 2010, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) [4] in 2012, the Royal College of Physicians (RCP) of London, United Kingdom [5] in 2007, and the German guidelines [6] in 2007. Various methods of prescribing the radioiodine doses are noted. First of all, in patients with GD, the absorbed radiation dose with the aim of restoring a euthyroid status is frequently 150 Gy, whereas the dose to achieve ablative therapy is 200–300 Gy [3,6]. The range of activities, corrected for thyroid size and 24 h radioiodine uptake, varies from 5.55 MBq/g [2] to a maximum of 8 MBq/g (4). The EANM [3] recommends an equation derived from Marinelli’s formula [7], while the ATA [2] recommends both methods: administration of a single fixed dose of 370 or 555 MBq or calculation of the activity using the formula: activity (μCi) = gland weight (g) × 150 μCi/g × [1/24 hour uptake on % of dose] [2]. More detailed calculations with precise dosimetry are infrequently used in the United States. UK guidelines [5] recommend the use of a single fixed dose of 400 to 600 MBq rather than precise dosimetry. However, all agree that the mean prescribed activities should vary between 200–800 MBq irrespective of the method used. Concerning TMNG, an absorbed radiation dose of 100–150 Gy (requiring about 3.7–5.5 MBq/g corrected for 24 h $^{131}$I uptake) and 150–200 Gy (equivalent to 5.5–7.4 MBq/g) are recommended respectively by ATA [2] and EANM [3]. A fixed dose between 500 and 800 MBq is recommended by RCP [5]. In Europe high activities (300–400 Gy) [3,6] are recommended in patients with TSN, whereas doses are lower in America: 5.5–7.4 MBq/g corrected for 24 h uptake (equivalent to 150–200 Gy) [2]. Fixed doses are often proposed, ranging from 370 to 740 MBq for ATA [2], 500 MBq for SNM [4] and RCP [5] if the nodule size ≤ 3 cm.

Therefore there are two general approaches:

- prescription of fixed dose regime to all patients [8–14];
- administration of calculated doses corrected for the gland size or dosimetric method in order to deliver an individual quantity of radioiodine to the thyroid [8,12,13,15].

According to the meta-analysis performed in 2009 [16], both methods result in an equally successful treatment outcome. However, the results should be analysed carefully due to the wide heterogeneity of the studies included.

Given these circumstances, we provided the first nationwide French survey assessing current practices in radioiodine treatment of thyrotoxicosis in order to explore the experience of practitioners.

2. Material and methods

To identify the used strategies in France, a questionnaire survey was sent by mail to 69 French nuclear medicine units in hospitals and cancer treatment centres known to treat thyroid disorders. The expected respondents were endocrinologists or nuclear medicine physicians. The survey asked questions about practices in 2012 relating to radioiodine treatment: objectives, method for calculating the dose for radioiodine therapy and factors influencing the activity administered, choice of radioisotope to explore thyroid function, and method of gland size measurement.

3. Results

3.1. Characteristics of respondents

The response rate was 72% ($n = 40$ units). The respondents represented endocrinologists and nuclear medicine physicians that were covering most regions of France. In 2012, the percentage of respondents who treated > 100, 51–100, 10–50 and < 10 patients for hyperthyroidism were 25%, 38% and 5%, respectively (7% did not respond).

3.2. Objective of treatment

For 33% of respondents, a successful treatment outcome was defined as obtaining euthyroidism, whereas an ablative result was the aim in 26% of respondents. In addition, 41% of respondents adapted the treatment’s aim to the patient’s comorbidities.
3.3. Antithyroid drugs and drug-interaction management

Antithyroid drugs are routinely used before radioiodine treatment. Mean discontinuation period before therapy was 7 days (range, 3–21 days). Data on previous treatments was requested by 75% of the physicians.

3.4. Practice details of $^{131}$I dose determination

3.4.1. Based on the type of method

Two kinds of protocols are established in France: fixed doses and calculated doses (Table 1).

3.4.1.1. Calculated doses. Respectively for GD and for TSN/TMNG, 40.0% and 27.5% of respondents used optimized doses. Methods were based mainly on dosimetric calculation using Marinelli’s formula (80%) or its variant. Factors influencing the prescribed therapeutic dose were principally those used in the formula. The first factor was thyroid uptake based on radioiodine uptake, which was used by 100% of clinicians with the tracers $^{123}$I (63%; mean activity ± SD: 10.7 ± 4.4 MBq [range, 5–18 MBq]) or $^{131}$I (27%; 3.5 ± 0.9 MBq [range, 2.7–5 MBq]). The second was thyroid volume (93%). The type of disease was also an important factor for 80% of respondents. In very few cases, objective and age were taken into consideration. Twenty percent of the respondents did not use Marinelli’s formula but simply adapted the dose to the thyroid size.

3.4.1.2. Fixed activities. Standard activities represented 60.0% (GD) and 72.5% (TSN and TMNG) of the prescribed doses. Overall, one third of physicians referred to several levels of doses when standard doses were proposed, depending on the patient’s characteristics. The physicians were asked questions about the factors influencing the dose level. Factors cited were the kind of disease (100%). The medians of administered radioiodine activities are respectively 370 MBq (range, 185–740 MBq), 555 MBq (range, 185–740 MBq) and 555 MBq (range, 296–925 MBq) for GD, TSN and TMNG. Detailed results are presented in Fig. 1. In the second instance, 59% of physicians took into consideration the thyroid volume and 52% the thyroid uptake, with the radioactive tracers $^{99m}$Tc (69%; mean activity ± SD: 119.7 ± 35.1 MBq [range, 95–190 MBq]) or $^{123}$I (27%; 11.7 ± 11.4 MBq [range, 5.55–37 MBq]).

3.4.2. Based on the type of disease

Although the practices surrounding the prescribed doses for TSN and TMNG were similar (percentage of calculated versus fixed doses, median of administered activity), management of GD varied according to the hyperthyroidism class. Indeed, some centres use fixed doses only for nodules and goitre’s treatment as it is usually described in the literature. However, most centres used to calculate the doses for GD treatment. Details of practices are reported in Tables 2 and 3. Our data show that calculated doses were prescribed less often than fixed doses whatever the type of disease.

3.4.3. Based on thyroid uptake

Thyroid scintigraphy was performed to evaluate iodine overload, thyroid uptake and/or gland size. Images were acquired in one or several uptake measurements after administration of $^{99m}$Tc, $^{123}$I or $^{131}$I. Details of thyroid uptake practices are reported in Table 4. Even if physicians used fixed doses, 97.5% performed thyroid scan and qualitative uptake to evaluate thyroid function before administration of the therapeutic dose. The mean period between scan and therapy was 6 days (range, 1–30 days). One nuclear medicine unit did not perform a scan and adjusted the dose according to the thyroid volume measured by ultrasound.

3.4.4. Based on thyroid volume

Thyroid volume was determined by ultrasound (51%), ultrasound and scan (18%), scintigraphy (26.5%) or palpation (4.5%). In other words, 69% of physicians measured thyroid volume by ultrasound.

### Table 1
Protocols for determining radioiodine treatment dose by disease.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Calculated activities</th>
<th>Fixed activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Toxic solitary nodule</td>
<td>11</td>
<td>27.5</td>
</tr>
<tr>
<td>Toxic multinodular goitre</td>
<td>11</td>
<td>27.5</td>
</tr>
</tbody>
</table>

$n$ = number of centres.
kinetics of a tracer iodine can be measured with $^{123}$I or $^{131}$I. A total of 12.8% of nuclear medicine units, which responded to our survey, chose the radiopharmaceutical $^{131}$I to perform the radioiodine uptake test. When radioiodine is used, the recommended activity is 1.85–7.4 MBq and images should be obtained at 16–24 h [18]. However, the use of this radiopharmaceutical has the disadvantage of high radiation doses to the gland caused by its long half-life (8 days) and its $\beta^-$ particle emission. Moreover, since March 2012, low activity capsules (only used to perform $^{131}$I uptake) are no longer available in France. As a result, liquid forms of $^{131}$I have to be prepared with higher risk of contamination and increased radiation dosimetry for medical personnel. This practice can be explained by the fact that radiiodine is the radiopharmaceutical that best illustrates the pharmacokinetics of the therapeutic treatment. Moreover, in France, $^{131}$I is gradually being abandoned in favour of $^{123}$I, which is a good substitute because of its shorter half-life (13 hours), a gamma photon suitable for imaging with no $\beta^-$ radiation. The activity recommended for a $^{123}$I uptake test is between 7.5 and 25 MBq with early measurements at 3–4 h and late measurements at 24 h [18]. Pertechnetate-99 m acts in the same way as an iodine isotope and is trapped by thyroid cells but is not organified in the gland. In the majority of cases, the uptake and imaging data provide all the information needed for the evaluation of thyroid function. The injected activities in France range from 74 to 190 MBq with an average of 120 MBq. These are similar to those recommended by the guidelines [18], which range from 75 to 370 MBq. $^{99m}$Tc has number of advantages, such as a short half-life (6 hours), short retention in the gland and no $\beta^-$ radiation, thus resulting in a lower radiation dose to the thyroid gland (10,000 times less than that of $^{131}$I), as well as to the whole body. It is also inexpensive, is readily available and the procedure is shorter (no measurement at 24 h).

In our survey, 97.8% of physicians performed thyroid uptake tests. A total of 43.6% used $^{123}$I and 12.8% $^{131}$I to determine the kinetics of iodine. The others, all prescribing fixed doses, used $^{99m}$Tc, though in all probability not to adapt the dose but to reveal a potential iodine overload before administering the therapy, as recommended by the EANM guidelines [3].

Assessment of thyroid volume is another of the parameters needed to establish the calculated dose. In our study, most physicians estimated gland volume by ultrasound (69%), which was found to be more accurate than clinical or scintigraphic estimation [19]. Therapeutic failures appear to be correlated with large thyroid volume in some papers [20–22], whereas in others

### Table 3

<table>
<thead>
<tr>
<th>Calculated dose 27.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosimetry</strong></td>
</tr>
<tr>
<td>TSN</td>
</tr>
<tr>
<td>TMNG</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
</tr>
<tr>
<td>TSN</td>
</tr>
<tr>
<td>TMNG</td>
</tr>
<tr>
<td><strong>Fixed dose 72.5%</strong></td>
</tr>
<tr>
<td><strong>One activity</strong></td>
</tr>
<tr>
<td>TSN</td>
</tr>
<tr>
<td>TMNG</td>
</tr>
<tr>
<td><strong>Two levels of activity</strong></td>
</tr>
<tr>
<td>TSN</td>
</tr>
<tr>
<td>TMNG</td>
</tr>
<tr>
<td><strong>Three levels of activity</strong></td>
</tr>
<tr>
<td>TSN</td>
</tr>
<tr>
<td>TMNG</td>
</tr>
</tbody>
</table>

*Activity cited by ≤ 2 respondents.

### 4. Discussion

The aim of hyperthyroidism treatment is to destroy sufficient thyroid tissue to cure hyperthyroidism and to obtain euthyroidism or hypothyroidism. Relief of hyperthyroidism is achieved within 3–12 months after $^{131}$I therapy in 50–90% of patients with GD. However, the success rate varies considerably between studies and is dependent on the definition of the outcome and on knowledge of several factors. No consensus exists either on the ideal outcome or on the optimal way to determine the radioiodine dose and that is why many protocols are used. These include various fixed doses (185, 259, 370 and 555 MBq) [8–14], as well as doses calculated on the basis of thyroid size, radioiodine uptake or the turnover of $^{131}$I [8,12,13,15]. To reduce concerns regarding radiogenic stochastic risks and radiation side effects, the administered dose should be as low as reasonably achievable. Over-treatment means unnecessary radiation exposure for the patient, which is obviously undesirable, especially for younger patients.

The difficulty in calculating the exact individual radiation dose is explained by the necessity to determine not only the absorbed dose, but at least three unknown parameters: maximum uptake, effective half-life and thyroid volume. The

### Table 4

<table>
<thead>
<tr>
<th>Characteristics of uptake tests performed by French physicians (n = number of centres).</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>$^{99m}$Tc-sodium pertechnetate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>$^{123}$I-sodium iodide</td>
</tr>
<tr>
<td>$^{131}$I-sodium iodide</td>
</tr>
</tbody>
</table>

More than 2 measurements: 1 h, 4 h, 24 h and 48 h.
no such correlation was found [13]. Peters et al. [23] demonstrated that in patients who received a calculated dose, except in those with a volume ≤ 15 mL, the size/outcome dependency was almost compensated. In patients receiving standard activity, on the other hand, success was inversely related to thyroid size.

The last parameter to determine is the deposited dose. Doses under 90 Gy were also correlated with high failure outcome [22,25]. The frequency of persistent hyperthyroidism is inversely correlated with the deposited dose (27% after 150 Gy, 23% after 200 Gy and 8% after 300 Gy [22]), but as expected, the higher the prescribed doses, the higher the percentage of patients who become hypothyroid [2,17].

Despite these potential benefits of calculated doses and the possibility of precise individualized doses, several studies have failed to demonstrate improvements in cure rate over fixed doses [12,13,23,24]. Thierens et al. [26] noted that patient-specific dose calculations in radionuclide therapy are difficult to perform and possibly subject to large errors. Dosimetric formulas take into account individualized iodine metabolism, but ignore several other factors also known to affect treatment outcome, such as patient characteristics (patients with large goitre, severe hyperthyroidism, the fact that men and younger patients are possibly less likely to respond to a single dose of radioiodine) [14,16,21], previous antithyroid drug therapy [27], individual thyroid metabolism fluctuations [16,28], or uptake thresholds for optimal therapeutic response. Therefore there is a large variety of methodologies to calculate individual dosimetry-based activity. In view of these considerations, it is uncertain whether calculated methods are optimal for determining administered $^{131}$I activities.

There is some controversy surrounding the question of whether hypothyroidism following radioiodine therapy is a complication or a negative outcome. Because of the availability of early and sensitive biological markers, and assays to diagnose post-$^{131}$I hypothyroidism and adjust hormone replacement by levothyroxine, hypothyroidism is often seen as an endpoint rather than a complication [29]. From this point of view, administration of standard ablative radioiodine activities is the quickest way to recover from hyperthyroidism. However, only 26% of the physicians who were questioned in our study expected hypothyroidism. This is why the use of calculated doses was shown to be more frequently attempted in France than in other countries. One explanation may be that many physicians (31% to 41%) do not administer an identical dose in all patients but adapt the prescribed dose according to different dose levels.

Even in the literature, a large range of activities for each thyroid disorder is described. For GD, low fixed doses (185 MBq) are associated with a reduced early incidence of hypothyroidism but often result in low cure rates (41.3%), whereas 370 MBq results in 60.8% of hypothyroidism [21]. As we know that geographical factors can influence outcome, we reviewed studies carried out at our latitudes. Metso et al. in Finland [14] found an 80% cure rate with the administration of a fixed dose of 259 MBq. In the UK [30], outcomes of patients given a single dose of $^{131}$I of 185 MBq, 370 MBq and 600 MBq were compared and the success rates (eu- and hypothyroidism) at 1 year were respectively 63%, 75% and 84%. However, an increased incidence of hypothyroidism was evident with higher doses (600 MBq: 60%; 370 MBq: 49%, $P = 0.001$; 185 MBq: 38%, $P < 0.001$). The outcome according to disease (GD versus TSN) was also compared. There was no significant difference in the cure rates following $^{131}$I treatment when comparing the etiology: hyperthyroidism was treated at 1 year for 76% of patients with GD and for 77% of patients with TSN but significant lower rates of hypothyroidism were noted in those with TSN (24% vs 4%, $P < 0.001$) [14]. Some clinicians now prefer to administer a large ablative dose (555 MBq and upwards), which results in early hypothyroidism, so that the need for long-term follow-up of thyroid function in euthyroid patient is obviated. However, concerns about the possible long-term effects of $^{131}$I and radiation exposure suggest the need for caution in increasing the amount of $^{131}$I administered to achieve an acceptable cure rate. It could also be argued that in some patients, a lower dose could be as effective as a standard fixed dose. Subjects unlikely to respond to standard doses or with good prognostic factors should therefore be identified in order to administer an optimized dose. In the other hand, patients with high cardiovascular risk, significant comorbidities or a long duration of hyperthyroidism, rapid relief of hyperthyroidism is usually mandatory. These clinical considerations may explain the frequent use of different doses regimen according to patients.

Worldwide, protocols used include various fixed doses and doses calculated on the basis of formulas or gland size. Practices are heterogeneous and, given their limited scientific foundation, most recommendations are unfocused, leading to a variety of clinical practices. The aim of this study was to collect data on French practices in order to determine the trends of prescription. The data from our present study demonstrated that practices were heterogeneous and subject to large variations. No data about cure rates were collected, so advantages in terms of outcome for the two methods could not be highlighted. Trends in clinical practices concerning radioiodine treatment were compared with a UK survey carried out in 2006 [31]. In both surveys, the majority of responders used a fixed dose of radioiodine (70% in the UK versus 60% in France). The range of fixed activities were similar (200–800 MBq in the UK versus 185–740 MBq in France) for GD but the median dose was higher in the UK (480 MBq) than in France (370 MBq).

5. Conclusion

Although $^{131}$I therapy for hyperthyroidism has been in use for more than 60 years, there are wide variations in every aspect of its administration to patients. Our survey documented the considerable diversity in the management of radioiodine dose determination, in the activities and doses administered. However, we can note that in France as worldwide, the majority of practices are based on the administration of a fixed activity, especially for TSN and TMNG treatment. For GD, a significant proportion of French physicians still use calculated doses. Most of the reasons given to justify the way radioiodine is administered are based on habit and local strategies. Another important point noted is the declining use of $^{131}$I, which was still frequently
used to perform thyroid uptake until 2012, when it stopped being available in capsule form in France.

There is currently a need for formal recommendations in nuclear medicine practices concerning the use of radiiodine in thyrotoxicosis treatment. This is particularly important given the potential toxicity of radiopharmaceuticals, complications of under- or over-irradiation, cost of health care, and emphasis on quality of care. This survey highlighted the trends among clinicians in France and provides the baseline data for exploring the evolution of French clinical practices.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References