Experience in the use of radioactive iodine therapy for hyperthyroidism in Nigerian patients. A study of twenty-two patients.

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Summary

This is a descriptive and follow-up study of the efficacy of radioiodine ($^{131}$I) in the treatment of hyperthyroidism in Nigerian patients, and is aimed at creating awareness about the therapy amongst medical practitioners in the West African sub-region. Twenty-two patients (13 female, 9 males) were seen with clinical and biochemical features of thyrotoxicosis, and were treated with $^{131}$I between 1991 and 1999. The age range was 31 to 60 years, with a mean age of 44.2 ± 1.8 years. The indications for $^{131}$I therapy were diverse and included its use as a first-line treatment for Graves' disease, thyrotoxic heart disease, recurrent thyrotoxicosis and failed antithyroid drug therapy. An incremental fixed-dose regimen was used in successive years, for different batches of patients. The duration of follow-up ranged from two months to nine years with a mean duration of 3.6 ± 0.5 years.

Three patients achieved euthyroidism, two patients needed a re-treatment with $^{131}$I because of persistent Hyperthyroidism. Nine patients developed hypothyroidism between two to 30 months of receiving $^{131}$I therapy. While seven other patients defaulted soon after the treatment and one patient who also had type 1 diabetes mellitus suffered a sudden death after two months.

In conclusion, our experience revealed similar outcomes as have been reported by other workers. Radioactive iodine was found to be a safe and effective treatment for hyperthyroidism in Nigerian patients, but a high rate of default precludes adequate long-term follow-up.

Keywords: Hyperthyroidism, Radioiodine therapy, Follow-up study.

Résumé

Il s'agit d'une étude descriptive ainsi qu'un examen de contrôle à l'égard de l'efficacité du radiiode ($^{131}$I) dans le traitement de hyperthyroïdie chez les patients nigérians. Elle est également pour but de susciter une prise de conscience sur la thérapie parmi les médecins qui se trouvent dans la sous-région de l'ouest Africain.

Vingt deux patients (13 femmes, 9 mâles) ont été recensés avec des traits thyrotoxicose clinique et biochimique et ont été traités avec ($^{131}$I) entre 1991 et 1999. La répartition de l'âge était de 31 à 60 ans avec l'âge moyen de 44.2 ± 1.8 ans. Les indications à l'égard de ($^{131}$I) thérapie étaient diverses, y compris son efficacité dans le traitement des maladies graves, la thyrotoxicose maladie de coeur, la thyrotoxicose récurrente et l'échec de la drogue thérapie de l'antithyroïdie. On avait administré une dose régime fixée qui accroît régulièrement dans des années successives pour les groupes diverses des patients. La répartition de l'examen de contrôle était de la durée de deux mois au neuf ans avec le moyen de durée de 3.6 ± 0.5 ans.

On avait noté la réussite de l'antithyroïdie chez trois patients. Deux patients avaient besoin du traitement à nouveau avec ($^{131}$I) à cause de HT Hyperthyroïdie récurrente. Neuf patients avaient contracté hyperthyroïdie entre deux à trente mois après l'administration de la thérapie ($^{131}$I). Alors que les sept autres patients ont fait défaut après le traitement, et un patient qui avait le type 1 diabète mellitus est mort soudainement après deux mois.

En conclusion notre épreuve personnelle a dévoilé les mêmes résultats que les autres chercheurs avaient dit. La Radioactiveiode est devenue un traitement inoffensif et efficace pour la maladie de hyperthyroïdie chez les patients nigérians, mais on doit remarquer que la fréquence de défaut était élevée et l'examen de contrôle à long terme est exigé.

Introduction

Hyperthyroidism (HT) comprises of conditions in which there are excessive amounts of thyroid hormone, which are derived from an overactive thyroid gland, circulating in the blood and tissues. There are many causes of HT but the most common are Graves' disease, toxic multinodular goitre and toxic adenoma.

The signs and symptoms of HT have been well described in the literature and standard textbooks. However, many of the typical findings may be masked or subtle especially in the elderly patients and thus are more likely to be misdiagnosed.

In the presence of florid clinical features of HT, laboratory tests documenting undetectable thyroid stimulating hormone (TSH) levels and increased radiiodine uptake (RAIU), increased serum total thyroxine (T4) and triiodothyronine (T3), with free thyroxine index (FTI) would serve as baselines for evaluation of therapy, rather than necessary diagnostic aids. But in milder or subclinical cases, the presence of goitre makes the diagnosis of HT likely and confirmatory tests assume greater importance. A number of highly effective therapeutic agents and approaches are used for the treatment of HT. These include antithyroid drugs, (ATD) which block hormone synthesis, and ablation of the thyroid gland either by surgery or by radioactive iodine.

Each therapy has advantages and disadvantages, indications and contraindications.

The use of radioactive iodine is the subject of this communication. Radioactive iodine ($^{131}$I) is a simple, effective and economical means of treating hyperthyroidism, and has received widespread acceptance as the treatment of choice for Graves' disease, especially in older patients. The therapy is indicated for toxic nodular goitre and is effective in curing HT in virtually all cases, given single or multiple doses. Some other indications for $^{131}$I include failed ant-thyroid drug therapy, recurrent HT after partial thyroidectomy or persistent HT after a previous dose of $^{131}$I. The mean limitation of $^{131}$I in the treatment of
younger patients stems from the persistent concern about its potential effect on the progyny of patients treated with this isotope. Thus far, there has been no evidence of increased genetic damage in the offspring, or risks of congenital abnormality in those who have been treated. There has also been no proven increased incidence of leukaemia, carcinomas of the thyroid or other tumours in the patient and/or their progeny. Hypothyroidism is the major undesired effect of therapy, especially after high doses, as it is difficult to gauge the dose required accurately even after measurements of tracer iodine uptake, thyroid size and the effective half-life of $^{131}$I in the thyroid gland.

There is paucity of report on the use of $^{131}$I in Africans in general. The reasons for this may include its non-ready availability, coupled with its very short half-life and the high cost of therapy. In this report, we present our experience of $^{131}$I treatment in twenty-two patients with HT of diverse aetologies.

**Subjects and methods**

This is a descriptive, follow-up study of patients who were diagnosed to have HT, based on clinical and thyroid hormonal results and had received radiiodine therapy at some point in their management. Twenty-two patients were recruited over a period of nine years (1991 to 2000). The following are the definitions utilised in characterising the patients.

**Definitions of criteria**

1. Hyperthyroidism (HT) was diagnosed when a patient had clinical and hormonal evidence of the disease.
2. Graves' disease was diagnosed as the aetiology of the HT when the patient had any of the following: (a) diffuse goitre with or without ophthalmopathy, (c) pretibial myxoedema, (d) elevated plasma levels of thyroid receptor antibodies.
3. Recurrent HT was diagnosed when clinical and hormonal features of the disease relapsed after a period of euthyroidism following carbimazole therapy for at least 12 months and on a patient who had undergone thyroidectomy.
4. Failed anti-thyroid drug therapy was diagnosed when a subject had frequent relapses of HT while still on the medication.
5. Radiation-induced thyrotoxicosis was defined as recurrence of clinical features and hormonal evidence of HT soon after radioiodine therapy (i.e. less than two weeks), especially if the pre-treatment hormonal concentrations were normal.
6. Lag-phase phenomenon was defined as persistent features of HT (0-12 weeks) after radiiodine therapy.
7. Persistent HT was diagnosed when the subject remained symptomatic and also had hormonal evidence of the disease three months after receiving radiodiode therapy.
8. Sub-clinical hypothyroidism was diagnosed when an asymptomatic subject was found to have an elevated thyroid stimulating hormone (TSH) concentration, with normal levels of T3 and T4.
9. Hypothyroidism was diagnosed in a subject according to standard criteria.

**Study protocol**

Newly diagnosed patients were commenced on ATD therapy, until $^{131}$I could be procured for a cluster of about four to six patients. Radioactive iodine was procured from Amersham International Plc, Buckinghamshire, England between 1991 and 1997, and later from AEC-Amersham (Pty) Ltd, Sandton, South Africa. After an appropriate counselling was given, an informed consent was obtained from each patient.

The dose of $^{131}$I given to each patient was either based on the estimated weight of the gland in those with thyromegaly (4.44 MBq - 7.4 MBq per gram of the thyroid gland (120 mCi - 200 mCi per gram)) or fixed doses of 155 MBq to 444 MBq, with higher doses in patients with severe hyperthyroid features. Patients were instructed to continue their carbimazole one week before reporting for the $^{131}$I therapy. High dose of glucocorticoids (prednisolone, 40 mg - 60 mg daily) was prescribed concurrently with $^{131}$I in patients who had Graves' disease with active ophthalmopathy. The steroid was continued for another six to eight weeks thereafter.

Blood samples for thyroid function tests were taken from each patient at diagnosis, on the day of $^{131}$I administration and after one month of $^{131}$I treatment, then every two to three months and thereafter at increasing intervals.

**Follow-up care**

Patients were followed up every four weeks for the first three months and thereafter less frequently if euthyroidism has been achieved. Those who developed hypothyroidism received thyroid (L-thyroxine) replacement, while patients who had radiation-induced HT and persistent HT were treated with carbimazole with or without a blocker.

A retreatment with $^{131}$I for persistent hyperthyroidism was undertaken in those who consented to the therapy.

**Evaluation of thyroid function**

Thyroid function was assessed by radioimmunoassay of serum total T3, T4 and TSH, at the Immunoassay Laboratories, Lagos, Nigeria using standard kits from ICN Biomedicals, Cospa Mesh, California USA. The reference ranges are 4.0-7.0 mU/L, T4 64.3-178 nmol/L, T3 0.77-3.2 nmol/L, except otherwise stated.

**Statistical analysis**

Results are presented as mean ± standard error of mean (SEM), except where otherwise stated.

**Results**

**Baseline clinical data of the patients**

Twenty-two hyperthyroid patients (13 females, 9 male) were treated with $^{131}$I, between 1991 and 1999 at the Eko Hospitals, Ikeja, Lagos. The age range was 31-60 years, with a mean age of 44.4 ± 1.8 years. Table 1 summarises the age distribution of the patients. The duration of disease before $^{131}$I therapy ranged from the three weeks to eight years, with a mean of 2.4±0.5 years. Eleven patients had classical Graves' disease, two of which had active ophthalmopathy. Six other patients were suspected to have Graves' disease on the basis of some

<table>
<thead>
<tr>
<th>Age range</th>
<th>Frequency (%)</th>
<th>Frequency (%)</th>
<th>10th (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Iodine</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>2 (9.1)</td>
<td>5 (22.7)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>40-49</td>
<td>4 (18.2)</td>
<td>5 (22.7)</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>50-59</td>
<td>3 (13.6)</td>
<td>1 (4.5)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>≥60</td>
<td>0 (0)</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Total</td>
<td>9 (40.9)</td>
<td>13 (59.1)</td>
<td>22 (100)</td>
</tr>
</tbody>
</table>

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accompanying autoimmune disorders, such as long standing diabetes mellitus, or being a first degree relative of a patient with Graves' disease. Two patients had toxic thyroid adenoma, while aetiology of HT was unidentified in three patients, due to limitations of investigations. The indications for ¹³¹I therapy are summarised on Table 2. The radioactive iodine guide activity administered ranged from 185MBq to 667 MBq at one treatment session, with a mode activity of 444 MBq.

### Table 2  Indications for radioiodine therapy in 22 patients with hyperthyroidism

<table>
<thead>
<tr>
<th>Indications</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment on GD</td>
<td>7(31.8)</td>
</tr>
<tr>
<td>Failed ATD</td>
<td>5(22.7)</td>
</tr>
<tr>
<td>Thyrotoxic heart disease</td>
<td>3(13.6)</td>
</tr>
<tr>
<td>Toxic thyroid adenoma</td>
<td>2(9.0)</td>
</tr>
<tr>
<td>First-line treatment in ANI</td>
<td>2(9.0)</td>
</tr>
<tr>
<td>Persistent HT after first dose of ¹³¹I</td>
<td>2*</td>
</tr>
<tr>
<td>Total</td>
<td>22(99.7)</td>
</tr>
</tbody>
</table>

*This number is not included in the total. The total in percentage is not 100 because of rounding up of the decimals

*ATD, anti-thyroid drug
*GD, Graves' disease
*HT, hyperthyroidism

Follow-up characteristics of the patients

In Table 3 are summarised the characteristics of the patients during the follow-up period. In the first three months after ¹³¹I therapy, four patients had persistent HT, all of whom had received a guide activity of 370MBq or less. Radiation-induced thyroiditis was observed in two patients, while larcophase phenomenon was seen in three patients. One patient who had Graves' ophthalmopathy, suffered a transient worsening of her eye disease after receiving ¹³¹I, however, this condition responded to systemic steroid therapy. Minor complaints of neck pain and throat discomfort were observed in four patients, while nine others experienced no untoward effects following ¹³¹I therapy.

The duration of post-radioiodine treatment for the patients ranged from two months to nine years, with a mean duration of 3.6±0.5 years. Six patients defaulted soon after the ¹³¹I therapy, however, information received from one of the referring doctors revealed that one of these patients had developed hypothyroidism, and has been commenced on thyroxine replacement. One patient who also had a type 1 diabetes mellitus died suddenly two months after receiving ¹³¹I.

Two patients apart from those mentioned above had persistent HT, and had received a guide activity of 444MBq each.

### Table 3  Outcomes of treatment with varying guide activities of radioiodine in patients with hyperthyroidism

<table>
<thead>
<tr>
<th>S/N</th>
<th>Dose of ¹³¹I (MBq)</th>
<th>Duration after ¹³¹I</th>
<th>Clinical Outcome</th>
<th>&lt;3 months &gt; 3 months</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>222</td>
<td>9 years</td>
<td>-</td>
<td>Hypo after 19 mths</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>2.</td>
<td>185</td>
<td>5 years</td>
<td>Persistent HT</td>
<td>-</td>
<td>ATD for 5 years</td>
</tr>
<tr>
<td></td>
<td>444</td>
<td>3 years</td>
<td>-</td>
<td>Sub-Hypo after 4mths</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>3.</td>
<td>185</td>
<td>7 years</td>
<td>Persistent HT</td>
<td>Eut after 2.5 years</td>
<td>ATD x 2.5 years</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>5 years</td>
<td>Persistent HT</td>
<td>-</td>
<td>ATD x 1 year</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>5 years</td>
<td>-</td>
<td>Sub-Hypo after 2.5 years</td>
<td>Defaulted after therapy</td>
</tr>
<tr>
<td>5.</td>
<td>370</td>
<td>5 years</td>
<td>-</td>
<td>Hypo after 5 months</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>6.</td>
<td>370</td>
<td>5 years</td>
<td>Persistent HT</td>
<td>-</td>
<td>Defaulted after therapy</td>
</tr>
<tr>
<td>7.</td>
<td>370</td>
<td>5 years</td>
<td>-</td>
<td>-</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>8.</td>
<td>444</td>
<td>4.5 years</td>
<td>Worsening of Ophthalmopathy</td>
<td>-</td>
<td>b-blocker, defaulted</td>
</tr>
<tr>
<td>9a.</td>
<td>444</td>
<td>3 years</td>
<td>Radiation thyroiditis</td>
<td>Persistent HT</td>
<td>ATD, b-blocker</td>
</tr>
<tr>
<td>9b.</td>
<td>444</td>
<td>1.3 years</td>
<td>Transient itchy eye</td>
<td>Sub-Hypo after 2 months</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>10.</td>
<td>444</td>
<td>3 years</td>
<td>Minor neck pain*</td>
<td>Euthyroidism</td>
<td>-</td>
</tr>
<tr>
<td>11.</td>
<td>444</td>
<td>2 years</td>
<td>Radiation thyroiditis</td>
<td>-</td>
<td>ATD x 2 weeks defaulted</td>
</tr>
<tr>
<td>12.</td>
<td>444</td>
<td>2.5 years</td>
<td>Lag-phase, minor neck pain*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13.</td>
<td>667</td>
<td>2.5 years</td>
<td>Minor neck pain*</td>
<td>Hypo after 3 months</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>14.</td>
<td>222</td>
<td>2 years</td>
<td>-</td>
<td>Hypo after 4 months</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>15.</td>
<td>444</td>
<td>2 years</td>
<td>-</td>
<td>Hypo after 6 months</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>16.</td>
<td>373</td>
<td>1.5 years</td>
<td>Minor neck pain*</td>
<td>-</td>
<td>b-blocker, defaulted</td>
</tr>
<tr>
<td>17.</td>
<td>407</td>
<td>1.5 years</td>
<td>-</td>
<td>Sudden death</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td>18.</td>
<td>529</td>
<td>2 months</td>
<td>Lag-phase</td>
<td>-</td>
<td>Defaulted</td>
</tr>
<tr>
<td>19.</td>
<td>373</td>
<td>1.5 years</td>
<td>-</td>
<td>-</td>
<td>Hypo after 11 months</td>
</tr>
<tr>
<td>20.</td>
<td>444</td>
<td>1.3 years</td>
<td>-</td>
<td>-</td>
<td>ATD for 9 months, EUT</td>
</tr>
<tr>
<td>21.</td>
<td>444</td>
<td>1.3 years</td>
<td>Lag-phase</td>
<td>Persistent HT</td>
<td>Hypo after 6 months</td>
</tr>
<tr>
<td>22.</td>
<td>444</td>
<td>1.3 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

22* Minor neck pain with throat discomfort
ATD, anti-thyroid drug
EUT, Euthyroidism
Hypo, Hypothyroidism
Sub-Hypo, Sub-clinical hypothyroidism
Of these six with persistent HT, only two agreed to a retreatment with a second dose of 131I, both of whom subsequently developed hypothyroidism. The remaining four patients were continued on ATD for varying duration. Two achieved euthyroidism after 9–30 months, one patient developed sub-clinical hypothyroidism after 30 months of ATD, which later progressed to overt hypothyroidism two years after discontinuation of ATD, while the fourth defaulted after two years.

Overt or sub-clinical hypothyroidism was observed from about two months to 19 months in eight other patients, giving an overall mean onset of hypothyroidism after 131I therapy to be 9.6 ± 2.8 months. Overall, only one of the twenty-two patients reviewed in this study, is still euthyroid, and has not developed hypothyroidism four years after her first dose of 131I therapy.

Discussion

Hyperthyroidism (HT) is a common endocrinological disorder which is reported to affect two percent of women and 0.2 percent of men. It was initially believed that HT was rare in Africans, as earlier workers in the region reported very few cases. In this series, 22 patients with HT were recruited out of several that had been treated with other modalities apart from radioiodine.

The diagnosis of HT was based on clinical and laboratory findings. Graves’ disease was the most common cause of HT in this series, accounting for 50 percent of the cases, with an additional 27 percent of those who were suspected to have the condition. Prevalence of up to 76 percent has been reported in Caucasians in Europe and North America with Graves’ hyperthyroidism.

As far as treatment is concerned, there are three principal treatments used for patients with HT: anti-thyroid drugs (ATD), radioiodine and surgery, all of which are effective, but opinions differ about indications for them, because no single treatment regularly results in permanent euthyroidism. Radioiodine therapy being unavailable in Nigeria, has not been frequently administered, hence local experience with this form of treatment is scanty. Certain difficulties had to be surmounted, before radioiodine could be successfully administered to patients in this local setting. The main problem had to do with the short half-life of radioiodine, which made the timing of its arrival after importation, and its guide activity at the time of administration to the patient very critical.

In this series, the indications and procedure for 131I administration were as suggested by the Royal College of Physicians of London. The initial regimen adopted was to administer a fixed dose of 150 MBq. The two patients who were given this dose of 131I were not cured of their HT. But with a higher fixed dose of 370MBq each, half of the recipients continued to be thyrotoxic. On the other hand, most of the patients who received 131I guide activity of 444MBq and above were either cured or developed hypothyroidism. From this study, the optimum guide activity of 131I that produced therapeutic cure in the patients was between 370 MBq and 444 MBq.

Some short term effects of 131I administration that were observed included radiation thyroiditis, lag-phase phenomenon and minor anterior neck pain with some discomfort in the throat. These observations were not unexpected, as they are well known effects of radioiodine therapy. The onset of hypothyroidism in less than six months after 131I administration in the patients was found to be dose-dependent, as has been reported by Kendall-Taylor et al, who found that 50 to 90 percent of patients who received large dose of radioiodine (>555 MBq) became hypothyroid within one year of receiving the treatment.

As regards ophthalmopathy in patients with Graves’ disease, the experience in this series was limited to three patients who had some degree of active ophthalmopathy before or after 131I therapy. Two of these did not receive prophylactic glucocorticoid therapy, and were found to develop transient worsening of their eye disease after radioiodine treatment. A similar observation has been reported by Taitelstedt et al. However, other workers such as Calissen and colleagues, and Sridana and colleagues, found no significant association between radioiodine therapy and development of ophthalmopathy in their studies. It has been postulated that aggravation of ophthalmopathy after therapy may be due to an immunological hyperactivity in the contents of the orbit because of some antigens shared with the thyroid gland, which are produced through TSH receptor antibodies in hyperthyroid patients. In line with this view, prophylactic glucocorticoid therapy has been found to have a protective effect on eye disease in patients with pre-existing ophthalmopathy who received radioiodine with concomitant administration of glucocorticoids.

The cause of sudden death, of one of the patients soon after therapy, could not be verified. She was brought in dead by her colleagues at work, who had very scanty information about the circumstances that led to her collapse in the office. She had Graves’ disease with type 1 diabetes mellitus. She was placed on propranolol, following her 131I therapy and was clinically stable until two weeks before her demise. She had a good glycaemic control as judged by her fasting blood glucose values. It is hypothesised that she may have suffered from a severe hypoglycaemia (the manifestation of which might have been blunted by the concurrent b-blocker administration). The possibility of a malignant ventricular arrhythmia could also not be ruled out. The relatives declined a postmortem examination.

One principal limitation of this study was the incomplete follow-up of the patients, which was due to a high rate of default. This type of experience in prospective studies in Africans has been widely encountered. It is hoped that improved living standards, affordable health care facilities, and better communication systems will serve to change the people’s attitude. As it is easier and cheaper to treat hyperthyroidism than hyperthyroidism, we do not consider that the therapy with radioiodine is harmful to the patients from this part of the world, where a high rate of default is usually experienced, irrespective of the modality of therapy (surgery or continuous use of a thyrotoxic drug for persistent hyperthyroidism/recurrence of HT after thyroidectomy of 131I therapy).

In conclusion, our experience in the use of radioiodine therapy for hyperthyroidism was limited, and our results have not been as good as those reported from other parts of the world.

Acknowledgment

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