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Original Article

Determination of administered activities for the treatment of Graves' disease with iodine-131: Proposition of a simplified dosimetric procedure

ABSTRACT

This prospective study included 35 patients suffering from Graves' disease (GD) clinically and biologically confirmed by endocrinologists, sent to the nuclear medicine department of CHU de Bab El Oued, Algiers for iodine-131 therapy. CHU de Bab El Oued is a tertiary hospital located in the center of the capital Algiers. The aim of this study is to propose a simplified dosimetric procedure which will initiate iodine-131 therapy of GD in particular and hyperthyroidism in general in Niger. The determination of the maximum uptake was performed with a Biodex external probe at 2 h, 4 h, and 24 h after the administration of 3 MBq of liquid iodine-131. The iodine-131 activities were determined using the Marinelli formula with a predefined effective half-life (T_e) of 5 days and subsequently extrapolated half-life with kaleidagraph software. The statistical analysis was performed using an excel sheet and analyzed using the software package Statistica 10 (stat Soft, Tulsa, USA). the male:female gender ratio was1:4.5 and the mean age was 42.56 years (±7.14). The body mass index was within normal range with a value of 25.25 kg^2 (±0.42) and the mean average thyroid mass was equal to 24.05 (±10.53) g. The mean uptake value at 24 h was 43.24% (±17.68%) meanwhile the maximum uptake value was 46.28 (±21.13%). The estimated effective half-life (T_e) was 5.44 days (±1.96) days which were different from the predefined T_e of 5 days. The mean activity determined with fixed T_e and 24 h uptake was 244.45 (±109.2) MBq and the mean activity calculated with both extrapolated T_e and maximum uptake was 452.22 (±381.9) MBq. Empirical determination of activity in the treatment of GD gives higher activities (1.5 times) to patients than dosimetric methods based on the determination of extrapolated effective half-life.

Keywords: Dosimetry, empiric activities, extrapolated effective half-life, optimization, planning, predefined effective half-life, uptake

INTRODUCTION

Oral administration of iodine-131 has been a commonly accepted procedure for the treatment of benign and malignant disorders of the thyroid since the 1940s.[1]

The geographical situation of Niger, a landlocked country without any maritime coast, makes it a zone of high iodine deficiency; reads thyropathies in general and goiters in particular.

In the Nuclear Medicine Department of the Institut des Radio-Isotopes (IRI) in 2016, 12,471 patients were registered among them, 7740 were referred for exploration of the thyroid gland, which correspond for more than 62% of the activity of the department.

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In Niger, hyperthyroidism is not unknown, but very often underestimated because of the accessibility to diagnostic centers. According to a study carried out mainly at the National Hospital of Niamey in 2005, Graves' disease (GD) represents 79.25% of hyperthyroidism, with a female predominance.[2]

In Niger, the first-line treatment for hyperthyroidism involves synthetic antithyroid drugs in general and carbimazole in particular. Although carbimazole provides good results, the high cost and length of treatment are factors in adherence to treatment. Not to mention that the carbimazole is frequently out of stock.

If the treatment of hyperthyroidism by Iodine-131 is widely used in Western countries, it is almost nonexistent in sub-Saharan Africa in general and in Niger in particular.

In therapeutic applications of nuclear medicine, patient-specific-dosimetric studies prior to the treatment are essential if one wishes to determine as accurately as possible the therapeutic activity necessary to deliver the desired radiation dose to the target tissue. The fixed activity approach also called empiric method takes into account neither the individual variability in the kinetic and morphological parameters of the structures to be treated nor those of the healthy tissues.[5]

In this study, an external Biodex probe was used for thyroid uptake measurement at several times and values were simulated with Kaleidagraph 4.0 from Synergy Software in order to obtain the maximum uptake which will be used to calculate the administered activities.

This paper presents the proposal of a simplified dosimetry procedure which will be implemented in the Nuclear Medicine Department of Radioisotopes Institute of Abdou Moumouni University in Niger.

MATERIALS AND METHODS

Patients and uptake measurement

Our research protocol has been approved by the national ethics committee for research in human health. All information was treated with anonymity and confidentiality, and documents were explored for scientific purposes.

In this prospective study, which 35 includes patients suffering from GD referred by endocrinologists to the Nuclear Medicine department of CHU de Bab El Oued, Algiers-Algeria for iodine-131 therapy. All these patients, whom were under anti thyroid drug, stopped their treatment at least one week before therapy. All females' patients under an age of 50 years received a pregnancy test (βHCG).

The gender ratio of 1 male to 4.5 females, an average age of 41.29 (±11.71) and a body mass index of 24.94 (±4.24) kg^2. The mass of the thyroid was determined by an echography using a three dimensional (3D) software for Midray DC-60 (Oriental Medical Equipment) Medical imaging system, China.

Initially, in this department, all patients referred for iodine-131 therapy of GD received a pretherapeutic dosimetry based on thyroid uptake measurement with a Biodex probe at 24 h after the administration of 3 MBq of liquid iodine-131 and activity will calculated with a predefined T_e of 5 days.

In this study, we performed uptake measurement at 2 h, 4 h, and 24 h after the administration of 3 MBq of liquid iodine-131 in order to determine the maximum uptake using Kaleidagraph software 4.0. Kaleidagraph is the tool for 2D analysis and visualization of experimental data. It is suitable for research, engineering and industry. User-friendly and powerful Grapher, it transforms data into a professional-quality graph.

The iodine-131 activities were determined using the Marinelli method with a predefined effective half-life (T_e) of 5 days and with a second method using the extrapolated T_e estimated by the Kaleidagraph software.

The calculation of the activity was done for each individual patient using the formula presented above (equations a and b).

Radiation protection recommendations were explained and applied to each patient regarding distance, duration of exposure, as well as avoidance of pregnancy for all women of childbearing age 6 months after therapy. For this purpose, a pregnancy test was carried out for all women of childbearing age before the therapy. The radiation protection of the patient was based on hygiene recommendations and common sense: hydrate well, have frequent urination, avoid contact, etc.

Methods

The iodine-131 activity to be administered was determined using the Marinelli formula with extrapolated T_e:[8]

$$A\ (\text{MBq}) = \frac{23.4 \times m(g) \times \text{Dose}\ (\text{Gy})}{\text{estimated uptake at } t = 0(\%) \times \text{Te}\ (d)} \quad (a)$$

And Marinelli formula with fixed T_e at 5 days, method used in the department:

$$A\,(MBq) = \frac{5\times\ m(g)\ \times\ Dose\ (\ Gy\ )}{Uptake\ \ at\ \ 24\ \ h(\ \%)} \quad (b)$$

Where A (MBq) = iodine-131 activity to be administered, 23.4 is the absorbed dose factor, 5 = predefined effective half-life which is equal to 5 days, m (g) = thyroid mass, Dose (Gy) = dose to be impacted to the thyroid, uptake (%) = fraction of iodine-131 in the thyroid at the time t, uptake at t = 0 is the maximum uptake and T_e is the effective half-time.

For both calculation methods, the target dose is 80 Gy.

The dosimetric method was based on the MIRD formula:[6]

$$(D) = \tilde{A}.\ S \quad (c)$$

Where (D) = mean dose to the target organ (Gy);

$\tilde{A}$ = cumulated activity into source organ (MBq);

S = mean absorbed dose to the organ per unit cumulated activity (Gy/MBq).

The time integrated activity taken up in thyroid, i.e., the cumulated activity, is:

$$\tilde{A} = \int_0^{\infty} A0.\ U(t)dt = A0.\frac{U0}{\lambda biol} \quad (d)$$

Where A0 is the administered activity and U(t) the thyroid iodine uptake curve derived by a bi-compartmental model and described in equation f.

Thyroid uptake measurement at 2H, 4H and 24H was made after the administration of 3 MBq of liquid iodine with a Biodex probe, then U(t) was determined using Kaleidagraph software and also the iodine-131 effective half-life extrapolated.

The thyroid uptake has been assessed with a probe equipped with a sodium iodide crystal of 5 cm diameter and 5 cm depth and shielded by 5 cm of lead. The distance probe detector to patient's thyroid is about 25 cm. At the time t, the uptake was calculated according to the following relationship:

$$U(t) = \frac{Cthy\ \ \text{-}Cbkg}{Csyn} e^{\lambda phy.t} \quad (e)$$

Where C_{thy} = counts per second (CPS) in the thyroid, Cbkg = CPS in the background which corresponded to the circulated activity, Csyr = full syringe measured by the probe and radioactive decay correction.[5-7]

Iodine kinetics described by iodine thyroid uptake (U) was assessed according to the following equation:

$$U(t) = \frac{U0.\lambda in}{\lambda biol - \lambda in}\left(e^{-\lambda in.t} - e^{-\lambda biol.t}\right) \quad (f)$$

(U_0 = percent fraction of administered iodine, which is transferred to the thyroid, λin = rate of the uptake, λbiol = rate of biologic decay).

RESULTS

The characteristics of 35 patients with GD who were referred to receive iodine-131 therapy are shown in the Table 1.

The extrapolated uptake and T_e found using kaleigraph software are >24 h uptake and predefined T_e, both differences were significant with $P < 0.05$.

There is also significant difference ($P < 0.05$) between activity calculated with predefined Te and activity calculated with extrapolated T_e, but empirical activity is much higher than both.

Activity calculated with extrapolated T_e is much correlate to empirical activity ($r = 0.61$, $P < 0.0001$) than activity calculated with predefined T_e ($r = 0.36$, $P < 0.0303$).

m = mass of thyroid, $IU_{24\ h}$ = iodine uptake for 24 h, ext. IU = extrapolated iodine uptake, EXT. T_e = extrapolated T_e, Act.(pred. T_e) = activity calculated with predefined T_e, Act.(EXT. T_e) = Activity calculated with extrapolated T_e, Emp. Act = empirical activity, Dose = dose impacted to the thyroid.

As shown in Figure 1, in the distribution of the 35 patients, two types of cervical uptake:

The uptake measured at 24 h and the maximum extrapolated uptake calculated by Kaleidagraph.

In our study, the maximum uptake extrapolated is in 85% (30 patients) higher than 24 h uptake.

As shown in Figure 2, we could see, in the distribution of the 35 patients, two types of effective half-life: the extrapolated one (Blue) and the predefined one (Red).

The mean effective half-life is 5.44 days with a minimum of 0.5 day and a maximum of 7.8 days. Figure 2 shows us variability of iodine-131 kinetics compare to the predefined T_e of 5 days.

Table 1: Characteristics of 35 patients with Graves' disease

	m (g)	$IU_{24\ h}$ (%)	Ext.IU (%)	Ext.T_e (d)	Act (pred. T_e) (MBq)	Act (Ext. T_e) (MBq)	Emp. Act. (MBq)	Dose (Gy)
Mean±SD	24.05±0.52	43.20±17.68	46.27±21.12	5.44±1.96	244.44±109.20	452.22±381.90	606.8±33.81	235.82±99.70

m: Mass of thyroid; $IU_{24\ h}$: Iodine uptake for 24 h; EXT.IU: Extrapolated iodine uptake; EXT.T_e: Extrapolated T_e; Act. (pred.T_e): Activity calculated with predefined T_e; Act. (EXT.T_e): Activity calculated with extrapolated T_e; Emp.Act.: Empirical activity; Dose: Dose impacted to the thyroid; SD: Standard deviation

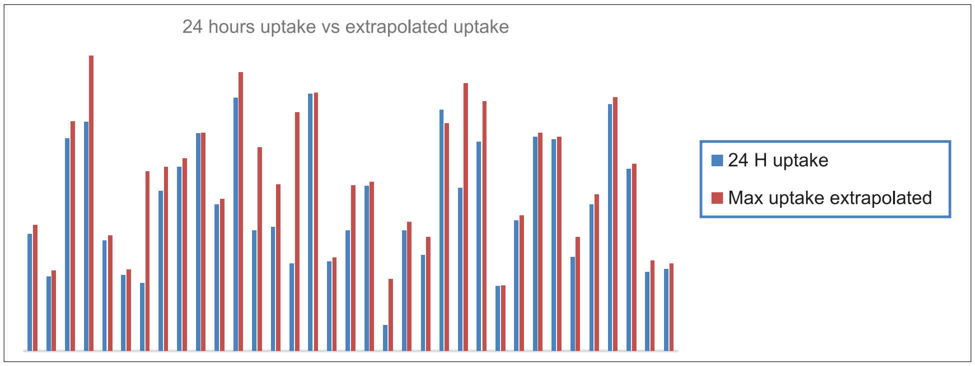

Figure 1: Twenty-four hours uptake versus max uptake extrapolated

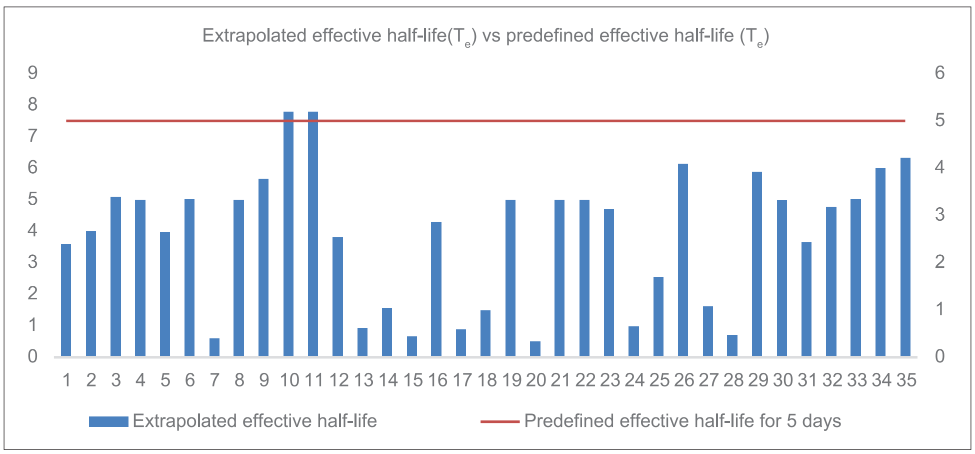

Figure 2: Predefined effective half-life andextrapolated effective half-life

In most cases, activities administered are much higher than activities extrapolated, but in eight patients, the extrapolated activity is high due certainly to the fall in the extrapolated T_e and the increase of the maximum uptake extrapolated in GD patients.

The mean difference of activities between predefined T_e méthod and extrapolated T_e method is– 208.94 MBq.

DISCUSSION

The radio iodine treatment of GD is very effective, safe, and simple to implement. It is the most frequent worldwide procedure of nuclear medicine therapy. It is performed most of the time in outpatient and needs however the full collaboration of the patient.

In our study, we used liquid iodine-131 instead of capsule because liquid iodine is very cheap. We are in the country with low income where everything is priority so we have chosen the generic over the specialty to treat the majority of the population, of course by applying the strict rules of radiation protection.

The importance of planning an individually tailored dose in metabolic radiotherapy in contrast to fixed-activity regimen, as recommended by the ICRU 67[3] and Euratom Directive 97/43[4] and was confirmed by variability of iodine kinetic parameters observed in the current study on hyperthyroid patients. However, to be approved, a dosimetric method for determination of the most appropriate radiopharmaceutical activity first must be tested through comparison of dosimetry-calculated parameters with effective variables measured in therapy. In the present study, two methods have been compared, one based on three uptake values (2 h–4 h–24 h) and one on the 24 h uptake and a predefined T_e of 5 days.

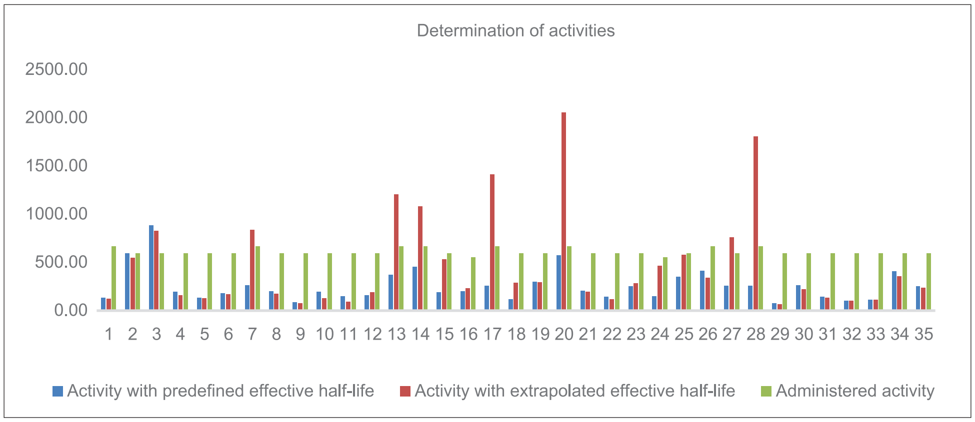

Figure 3: Determination of activities: Predefined T_e method (Blue), extrapolated T_e method (Red), Empirical Method (Green)

In order to determine the activity to be administered in GD therapy, the thyroid mass, thyroid uptake and the effective half-life (T_e) are the main variable to be determined or estimated. Those parameters also depending on the decided amount of radiation delivered dose to the thyroid gland taking into consideration the irradiation of other organs.[5,6]

In this study, as usual, female patients were the most frequent with a gender ratio of 1 male for 4.5 females and an average of 42.65 years, which is also casual[10] since GD appears the most often in adult patients.

In 35 GD patients studied, the mean 24 h uptake was 43.24 (±17.68%) and the maximum uptake calculated by Kaleidagraph was equal to 46.28(±21.13%). The maximum thyroid uptake is in the most cases higher than the 24 h uptake. About 88% of the extrapolated thyroid uptake ($P < 0.05$) was higher than 24 h uptake which will influence the activity calculation.

The calculated effective half-life (T_e) was 5.44 (±1.96) days which is significantly longer that the predefined T_e, which was of 5 days. In our study, the extrapolated T_e differs with a range from 0.5 to 7.8 ($P < 0.005$).

In many publications,[7-11] the range of calculated T_e was varying from 4.4 days (Berg *et al*.) to 6.95 days (Willegaignon *et al*.) with intermediate values of 5.18 days for (Hyer *et al*[12] These calculations are subject to individual physio-pathologic variations and the discontinuation or otherwise of the antithyroid drugs.

The effective half-life may differ, with a range from 1.6 to 7.5 days, which will contribute to a greater error with a factor of 4.6 in the formula than that expected from thyroid volume which is estimated to be a factor of about 1.5 and is considered a significant source of error.[13]

The mean activity determined with predefined T_e and 24 h uptake was 244.45 (±109.2) MBq and the mean activity [Figure 3] determined with calculated T_e and maximum uptake was 452.22 (±381.9) MBq.

The mean difference of activities between predefined T_e method and extrapolated T_e method was 208.94 MBq ($P < 0.05$). This results show that the activity calculated with extrapolated T_e is much higher (almost the double) than the activity determined with predefined T_e. This fact demonstrates that the predefined T_e is not an appropriate solution because of large variation with the real one as quite often reported by the literature.[5-11]

The limits of this study undoubtedly remain the size of the sample, the time devoted to collecting the data and finally the failure to take into account the activities calculated, then administer them to patients to compare the two dosimetric methods in patient monitoring. The next step is therefore to implement the procedure in the nuclear medicine department of the IRI and then continue this study on a much larger sample.

CONCLUSION

This study shows that the dosimetric method based on the thyroid uptake of Iodine-131 determination on 3 points (2 h, 4 h, and 24 h) and further estimation of the effective half-life present good correlation ($P < 0.05$) between kinetics and the delivered target dose to the thyroid gland. This method may also allow giving higher activity when taking into consideration the extrapolated maximum activity.

The determined activity with 3 points method (2 h, 4 h and 24 h) is lower than the one defined by the empirical method activity but higher than 24 h uptake method.

For low-income countries, with only one center, wishing to practice personalized dosimetry, this model is suitable for treating GD with iodine-131, because it permits in 24 h to have a dosimetry based on three points (2 h, 4 h, and 24 h) and to administer the calculated activity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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