COMPARISON BETWEEN THE EMPIRICAL AND MATHEMATICAL METHODS IN THE ADMINISTRATION OF RADIOIODINE IN HYPERTHYROIDISM

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ABSTRACT: The aim of the study is to demonstrate the utility of a personalized formula in order to calculate the optimal activity to be administrated with the intention to treat hyperthyroidism, in comparison with the empirical method where fixed activities are administrated to the patients with hyperthyroidism. The result showed that the individual dose addicted to the mathematical method succeed in the hyperthyroidism in 29 cases comparative to 23 cases.
KEYWORDS: hyperthyroidism, radioiodine, empirical method, personalized calculation method, recurrence.

1. INTRODUCTION

Radioiodine (I-131) was the first radiopharmaceutical used to treat hyperthyroidism (HP), the first procedure being performed in the 1940s [CMF13, Pic12]. Besides radioiodine therapy there are also other alternatives to treat hyperthyroidism: anti-thyroid drugs therapy and surgery. Usually, the first-line therapy consists in medical treatment with administration of anti-thyroidal medication with the intention to stabilize the symptoms of the patient and, as a second therapeutic step - if the disease evolution or recurrence requests it - radioiodine could be an option to complete the HP treatment. In some centers, radioiodine therapy represents the first-line option to treat hyperthyroidism. Surgery may also be a therapeutic option in HP, but this alternative is reserved for the cases of large hyperthyroidized goiters or in the case of thyroid nodules with high suspicion for later malignant degeneration. The purpose of radioiodine therapy in patients with HP is to achieve a non-HP status, which can be either euthyroidism or HP, in the later situation being necessary substitutive thyroid hormonal treatment. Radioiodine is commercially available under the form of radioactive capsules with different activities according to the characteristics given by different producers or as radioactive liquid solution of (I-131) NaI, orally administrated in nuclear medicine departments specialized and authorized by national authorities to manipulate radioactive sources of I-131 with therapeutic purposes.

Table 1. Physical data of I-131

I-131	
$T_{\frac{1}{2}}$ physical	8.04 days
$T_{\frac{1}{2}}$ biological	120-138 days
$T_{\frac{1}{2}}$ effective	7.6 days
Γ energy	364 KeV (81.8%abudance)
β^- energy	606KeV (89.7%abudance)

I-131 is a radioactive isotope with a physical half-life of 8.05 days (193 days). It decays by gamma emissions with an energy peak of 364 keV and by particulate emissions, beta$^-$ particles with and average energy of 606 keV (Table 1). The beta$^-$ particles are responsible for the curative effect due to their physical properties related to the interaction with matter: the particles deposit their energy in the tissues within a range of 2.2 and 3.1 mm causing cell death and destruction of hosting thyroid cells [Pic12, L+08, V+11].

The typical activities used in HP treatment may vary between 3mCi and 30mCi, but the administrated activity may be adjusted according to the clinical status and the protocol used for treatment. There are two methods used for radiopharmaceutical administration. The first method consists in the administration of empirical fixed activities and it is the most used method [A+13, D+13]. The second method is more accurate, being a calculation method based on calculations designated to obtain a more accurate estimation of the necessary activity to be administrated to the patient in order to achieve the desired therapeutic effect and to minimize the irradiation of the patient. The aim of the study is to demonstrate that the formula used in our department to calculate the administrated activity to the patients diagnosed with HP increases the therapeutic success and reduces the chances of disease recurrence in comparison with the empirical method.

2. PATIENTS AND METHODS

The study was performed in the Nuclear Medicine department of the Oncology Institute "Prof. dr. Ion Chiricuţă" Cluj-Napoca, over a period of 18 months. We included in our study 60 patients with HP who received radioactive iodine treatment (iodine-131, ^{131}I). Before iodine treatment each patient underwent a clinical evaluation with laboratory testing, thyroid ultrasound, thyroid scintigraphy and/or a radioactive iodine uptake test and stopped the hormone medication with 5-7 days before. Radioiodine was orally administered in the form of capsules.
The patients were divided into two groups. First group G1 consists of 30 patients (27females and 3 men), who received personalized activities calculated by using the following formula:

$$MBq=(V\times 25\times Gy)/(RAIU(24h)\times T\_ef) \quad (1)$$

where MBq = the calculated activity in MBq, V = the gland volume estimated at ultrasound in ml (cm^3), Gy = the estimated dose at thyroid level, $RAIU(24h)$ = % of thyroid uptake at 24 h, T_{ef} = effective half-time, and 25 is a constant[PVH13].
The second group G2 consists of 30 patients (26 females and 4 men), who received fixed activities.
The calculated activities vary from the available fix activities of radioiodine capsules. In order to administrate the desired calculated activity it is necessary to calculate the moment the activity will reach the desired value, in relation with the activity in the day when the capsules are calibrated. For this we calculate:

$$D_F = \frac{A_{calculated}}{A_{calibration}} \quad (2)$$

Table 2. Physical Decay of I-131

Days	Decay factor (D_f)	Days	Decay factor (D_f)
0	1	11	0.387
1	0.917	12	0.355
2	0.842	13	0.326
3	0.772	14	0.299
4	0.708	15	0.274
5	0.650	16	0.252
6	0.596	17	0.231
7	0.547	18	0.212
8	0.502	20	0.178
9	0.460	24	0.126
10	0.422	30	0.075

The calculated activities vary from the available fix activities of radioiodine capsules. In order to administrate the desired calculated activity it is necessary to calculate the moment the activity will reach the desired value, in relation with the activity in the day when the capsules are calibrated. For this we calculate:

$$D_F = \frac{A_{calculated}}{A_{calibration}} \quad (3)$$

Using the table 2 we can calculate when (after how many days) the capsule will reach the desired activity and may be administrated to the patients. (Table 3).
The patients were evaluated at six months after the iodine treatment. In the G1 29 patients were cured and just 1 patient needed additional radioiodine treatment. For the G27 the patients needed additional radioiodine treatment and 21 patients were cured.
In order to describe the variables we applied descriptive statistical methods (mean ± standard deviation, confidence intervals, maximum/minimum values) and for the analytical statistical data we submitted the data to the Student "t-Test" for independent samples.
For the statistical processing we used dedicated statistical applications: SPSS and Statistica 6.0. For both groups, we calculated, with standard deviation and confidence interval for age and iodine administered quantity values. We analyzed the frequency and the characteristic of qualitative variables (sex of the patients and the frequency of recurrence). We calculated the odds ratio for the recurrence occurred in the two groups to analyze how the used method influences the therapeutic success or failure.

3. RESULTS

For the G1 the average age expressed in years was 48.30±15.89with a minimum of 22 and a maximum of 81, half of the group of patients having the age under 47. The age distribution is uniform without a unique module. The administered average activity expressed in Mbq was 313.39±38.03:IC (299.18-

327.59) with a minimum of 185 and a maximum of 366.3 for half of the patients being under 336.7. The value distribution is non-uniform with unique module 33.3 and 3 extreme values. For the G2 the average age expressed in years was 50.90±15.81:IC (45-56.80) with a minimum of 27 and a maximum of 82, half of the group of patients being under age 52. The age distribution is uniform without a unique module. The average activity administered in MBq was 252.58±82.82:IC (222.39-282.778), with a minimum of 99.90 and a maximum of 432.90, half of the patients being under batch 336.70 (Figure 1). The values distribution is uniform without a unique module and the most common value being reported for 140 MBq, 259 MBq and 336.7 MBq (Table 3).

Table 3. Characteristics of mean values for the parameters analyzed in patients in G1and G2

	N (%)	media ± SD (95% IC)	minimum – maximum (median)
G1			
Age (years)	30 (100%)	48.30±15.89 (42.36-54.52)	22-81 (47)
Average activity (MBq)	30 (100%)	313.39±38.03 (299.18-327.59)	185-366.3 (336.70)
G2			
Age (years)	30 (100%)	50.90±15.81 (45-56.80)	27-82 (52)
Average activity (MBq)	30 (100%)	252.58±82.82 (222.39-282.778)	99.90-432.90 (259)

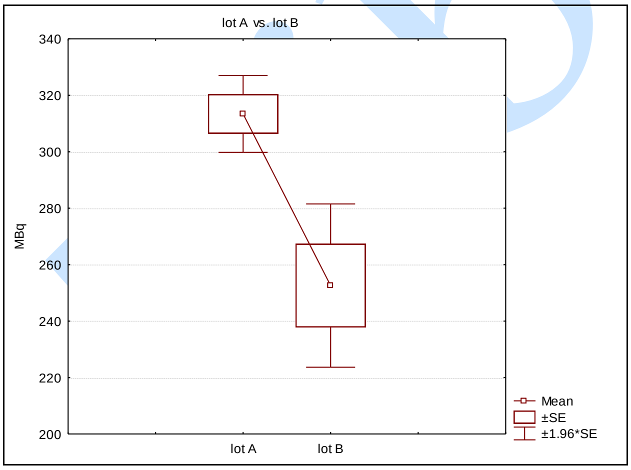

Figure 1.The difference of the median ± SE for radioiodine (MBq) administered to patients in G1 and G2

It was noted a difference with strong statistical significance between the average administrated activities of iodine for the G1 in comparison with G2 (Table 4).

Table4. The difference of the values of the iodine (MBq) administered to patients for G1 comparative to G2

media	"p" G1 vs G2
I-131 (MBq)	0.0004**

Table 5. The frequency of cases in G1 and G2, regarding to gender

Gender	G1 N=30 (100%)	G2 N=30 (100%)
female	4 (13.33%)	3 (10.00%)
male	26 (86.66%)	27 (90.00%)

The gender distribution within the groups is quite similar: 4 females (13.33%), 26 (86.66%) for G1 and 3 females (10%), 27 (90%) for G2 (Table5).
The recurrence of disease is higher for G2 (23.33.0%) in comparison with G1 3.33% (Table 6).

Table 6. The frequency of cases in G1 and G2, regarding recurrence

Recurrence	G1	G2
yes	1 (3.33%)	7 (23.33%)
no	29 (96.66%)	23 (76.66%)

Table 7. The odds radio regarding recurrence for the patients in G1 in comparison to G2

	G1	G2
Cases with positive outcome	29	21
Cases with negative outcome	1	9
Odds ratio	8.82 [95%CI:1.01-76.96]	
Z statistic	1.87	
P	*0.04*	

The odds ratio (OR) regarding the recurrence in the two groups is 8.82 and the 95% of coincidence interval of OR is between 1.01 to 76.96. The statistical significance is important, with p=0.04 (Table 7).
Or, value showed that in G2 the recurrence is higher comparative to G1 which demonstrates the superiority of the method with personalized calculated activities, because it has a higher success rate.

4. DISCUSSIONS

After oral administration of capsules, sodium iodide is absorbed rapidly into the bloodstream and concentrates in the thyroid, where is incorporated into hormones which are stored in the intra-follicular colloid. The therapeutic effect depends upon the beta emission and the range over which these particles are effective. This is approximately 400-2000μm which considerably exceeds the follicular diameter (15μm). Consequently both the cytoplasm and nucleus are irradiated, as are adjacent follicles. Various workers have investigated the effects of radioiodine therapy and it is apparent that irradiated cells continue to contribute to the biochemical function of the gland but loses the ability to undergo mitotic cell division. Thus, the total gland mass is steadily reduced. [G+13, B+13b].

Usually the first line treatment for HP consists in the administration of anti-thyroidal treatment, but the major inconvenience of this treatment is its hepatic and hematologic toxicity and its carcinogenetic risk. This is the major reason why, after the HP symptoms are ameliorated the patients undergo radioiodine treatment [B+13a, A+13]. The aim of this treatment is to remove HP and to prevent as much as possible the recurrence of the disease.

The results presented demonstrate that for G1, where the calculation formula was used the recurrence is lower, in comparison with the G2 where the empirical method has been used. The difference with strong statistical significance ($p = 0.0004 < 0.05$) between the average administered activities for G2 in comparison to the average dose administrated for G1, stressed that for G2 where we used empirical administrations, the administrated activities are different in comparison with G1. This difference is not coincidental; it is related to the two different modalities to estimate the necessary administrated activities, the empirical method for G2 and the personalized calculation method for G1.

In G1 the administrated activities are higher in comparison with G2, but the values respect the European recommendations and the justification and optimization principles of radiation protection.

CONCLUSIONS

The purpose of radioiodine treatment for HP is to remove the HP symptoms and to prevent the recurrence of the disease, leading the patients into a state of non-HP. The therapeutic success is assessed related to the number and the frequency of recurrence. According to the result we may conclude that the presented personalized calculation formula for the administrated radioiodine activities in hyperthyroidism is an efficient method that improves the clinical response of patients undergoing radioiodine treatment for HP.

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