Errors in the absorbed and the administered ^{131}I therapeutic dose in patients with Graves' disease. A suggested more precise technique

Yangchun Chen[1] MD, PhD,
Jincheng Huang[1] MD,
Yuehui Wang[1] MD,
Sipei Xie[2] MD,
Fang He[3] MD

1. Nuclear medicine department of Quanzhou
2. Ultrasound department of Quanzhou
3. Endocrine medicine department of Quanzhou, 1st Hospital of Fujian Medical University Quanzhou City, China

Keywords: Radioiodine uptake - Effective half-life - Residence time - Absorbed dose

Corresponding author:
Yangchun Chen MD, PhD
East Road 248#, Licheng District, Quanzhou City, China, 362000
1526797743@qq.com

Received:
30 August 2017
Accepted revised:
13 November 2017

Abstract

Objective: The aim of this study was to evaluate the relative error (RE) in the thyroid absorbed dose (TD) of iodine-131 (^{131}I) in patients with Graves' disease comparing the simplified Quimby-Marinelli-Hine formula method (sQMHF) and the Standard Operational Procedures for dosimetry (SOPD) recommended by the European Association of Nuclear Medicine. **Patients and Methods:** This study included 45 patients with Graves' disease 12 men and 33 women; age 44.1±12.8 years. Thyroid mass (TM) was measured using ultrasound. Uptake of ^{131}I (RAIU) was tested at 2, 4-6, 24, 48-72, and 96-168h after its administration and the half-life ($T_{1/2eff}$) and resident time (RT) of ^{131}I were computed. According to the sQMHF, a prescribed TD of 75Gy required 3.7MBq/g of ^{131}I, correction based on the $RAIU_{24h}$ and $T_{1/2eff}$. Subsequently, the therapeutic TD was computed according to the SOPD and the RE was recorded. The data were analyzed using t-tests. **Results:** The TM, $RAIU_{24h}$, therapeutic TD, and RE were 36.5±23.9g, 0.54±0.14, 89.4±9.4Gy, and -0.01±0.02, respectively. There was a significant difference (t-value 9.84, P<0.01) between the prescribed and therapeutic TD because the sQMHF ignores the absorbed dose deposited in the thyroid during the first 24h, which is included in the SOPD. In addition, the RE was significantly smaller than the variable coefficient (VC) of the therapeutic TD (t=-39.6, P<0.01). **Conclusion:** When the activity of ^{131}I was calculated using the simplified Q-M-H formula, the therapeutic absorbed thyroid dose was significantly higher than what was expected for the prescribed dose. Precision of the individualized therapeutic absorbed dose could be improved by computing the activity of ^{131}I using the standard operational procedures for dosimetry of the EANM

Hell J Nucl Med 2017; 20(3): 217-221 *Epub ahead of print: 27 November 2017* *Published online: 11 December 2017*

Introduction

Iodine-131(^{131}I) is the first-line treatment for hyperthyroidism in adults with Graves' disease [1-4]. Up to a level, the higher activity of the administered ^{131}I, the higher the cure rate of hyperthyroidism [2]. According to the simplified Quimby-Marinelli-Hine formula method (sQMHF), the thyroid absorbed dose (TD) is determined based on the ^{131}I activity, thyroid mass, radioiodine uptake (RAIU) at 24h, and the half-life time ($T_{1/2eff}$) of ^{131}I in the thyroid [5]. That is to say, the higher the ^{131}I activity, the higher the TD received. However, the clinical results of some cases that received 131I doses determined using clinical formulae did not match the physician expectations [6-7]. We hypothesized that the TD error might be too large to cause this situation; therefore, this study evaluated the relative error (RE) of TD calculated using the sQMHF.

Patients and Methods

Participants

Patients with Graves' disease treated with ^{131}I in our department from December 2013 to April 2017 were included in this retrospective study. The inclusion criteria were a low-iodine diet for two weeks before the RAIU test, discontinuation of methimazole for ≥3d of propylthiouracil for ≥14d before the RAIU test [1], age ≥20 years [2] and the last RAIU measured ≥4d after administration [8]. Pregnant and lactating women were excluded. A total of 45 patients (33 women and 12 men. 44.1±12.8 years), were included in this study. All patients signed an informed consent before receiving treatment.

Thyroid mass measurement

The thyroid volume was measured using an ultrasonography scanner (iU-Elite, Philips) with an 8.5MHz linear array transducer and computed using the ellipsoid volume formula as previously described [9]. As the density of thyroid tissue is approximately 1.0g/mL, the thyroid mass was thus numerically equal to its volume in these units [1].

RAIU and $T_{1/2eff}$ measurement

A total of 50μL of ^{131}I solution, with activity ranging from 74 to 185kBq, was drawn using a Finnpipette® F1 single channel variable volume (5-50±0.5μL) pipette (Thermo Fisher Scientific, Finland), and dropped into each patient's mouth. Another 50μL of that solution was dropped into a tube that contained 25mL of water as a standard source. The patients fasted for 2h before and after the ^{131}I administration. The RAIUt tests were performed using a thyroid probe (Beijing Hehai Advanced Technology CO. LTD, China) at 2, 4-6, 24, 48-72 and 96-168h after administration [10].

$$RAIU_t = \frac{ThyCounts_t - Bg_t}{(StaCounts_t - Bg_t)\cdot e^{0.693\,t/24/8}} \qquad (1)$$

ThyCountst: thyroid counts at time t, Bg_t: air counts at time t and $StaCounts_t$: standard source counts at time t. $RAIU_{24h}$ and the last RAIU ($RAIU_l$) were used to determine the $T_{1/2eff}$ in the one compartment model, recorded as $T_{1/2eff}$_Q [11]:

$$T_{1/2eff}\_Q = \frac{(t_l - 1)\cdot \ln(2)}{\ln(RAIU_{24h}) - \ln(RAIU_l)} \qquad (2)$$

The RAIUl was not measured until 4d after ^{131}I administration [8].

Calculation of ^{131}I activity

In China, Europe, and the United States, 2.6-4.4, 3.7-5.6, and 5.6MBq of ^{131}I per thyroid gram, respectively, are typically administered for Graves' disease [1-3]. A fixed dose per thyroid gram; i.e. 3.7MBq, was prescribed using formula (3) in this study [5],

$$A(MBq) = \frac{3.7(MBq/g)\times M(g)}{RAIU_{24h}\quad (T_{1/2eff}\_Q/5)} \qquad (3)$$

where A=prescribed ^{131}I activity, M=thyroid mass and the $T_{1/2eff}$_Q was corrected for 5 days.

Calculation of residence time (RT) and TD

According to the sQMHF, the RT could be calculated by formula (4), and recorded as RT_Q [12].

$$RT\_Q = 1.44\,T_{1/2eff}\_Q \times RAIU_{24h} \qquad (4)$$

According to the converted sQMHF [5], the TD could be calculated using the following formula (5)

$$TD(Gy) = \frac{4.05\times A(MBq)\times T_{1/2eff}\_Q(d)\quad RAIU_{24h}}{M(g)} \qquad (5)$$

When A is substituted for the right side of the formula (3), we can see that the prescribed TD is identical to 75Gy as long as 3.7MBq ^{131}I per gram is administered and is not relevant to the thyroid mass.

The area under the curve (AUC) of the RAIU was computed using a two-compartment model solved via a least-square curve fit [13]. The AUC was equal to the RT, recorded as RT_S; i.e. formula (6), as described in the SOPD prior to radioiodine treatment of benign thyroid disease that was recommended by European Association of Nuclear Medicine (EANM) [8, 12]; the RE of the personal RT_S was recorded. And the $T_{1/2eff}$ calculated using the method of SOPD was recorded as $T_{1/2eff}$_S [8].

$$RT\_S = \int_0^{\infty} RAIU(t)\,dt \qquad (6)$$

The average energy, $\bar{E}$, deposited in the thyroid per decay of ^{131}I [8]; is a constant for each thyroid and is associated with the thyroid mass, as described in detail in reference 8.

$$\bar{E} = \frac{M^{1/4}+18}{7.2}\,\frac{Gy\cdot g}{MBq\cdot d} \qquad (7)$$

Thus, the personal therapeutic TD can be calculated using the following formula (8), described in the SOPD [8].

$$TD = \frac{\bar{E}\cdot A\quad RT\_S}{M} \qquad (8)$$

Finally, the RE of the personal therapeutic TD was equal to the RE of the personal RT_S.

Statistical Analysis

The activity of the prescribed ^{131}I was calculated using formula (3) and then the personal therapeutic TD was computed using formulas (6)-(8) following the SOPD [8]. The results were analyzed using Student's t-tests. P<0.05 was taken as an indicating a statistically significant effect.

Results

The average thyroid mass, $\bar{E}$, and $RAIU_{24h}$ were 36.5±23.9g, 2.83±0.05Gy • g • d^{-1} • MBq^{-1}, and 0.54±0.14, respectively. The average $T_{1/2eff}$_Q and $T_{1/2eff}$_S were 3.47±0.89d and 3.65±0.96d. There was not significant difference between them (t=1.22, P >0.05). As we know that $T_{1/2eff}$ is high correlation with RT. When $T_{1/2eff}$_S>$T_{1/2eff}$_Q (n=21), RT_S was larger than RT_Q (shown in Figure 1). When $T_{1/2eff}$_S=$T_{1/2eff}$_Q (n=3), RT_S was also larger than RT_Q (shown in Figure 2), because the RT calculated using the sQMHF only included the area under the curve from 1d to infinity and ignored the area under

the curve during the first day. When $T_{1/2eff}$_S<$T_{1/2eff}$_Q (n=21), it was relatively complex. RT_S may also larger than RT_Q (n=17), or may not larger than RT_Q (n=4) (shown in Figure 3). Thus, the RT_S (3.15±1.14d) was significant larger than RT_Q (2.92±1.01d) (t=8.78, P<0.01).

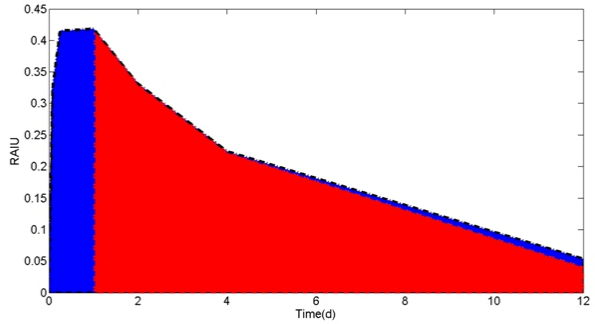

Figure 1. A female patient with $T_{1/2eff}$_S (3.87d)>$T_{1/2eff}$_Q (3.33d). The area under the curve from 1d to infinity calculated by SOPD and sQMHF was presented as (blue+red) and red region. It is obvious that her RT_S (2.61d)>RT_Q (2.01d). (In fact, the time would extent infinity, however the infinity is hard to present, the last time point was set as day 12).

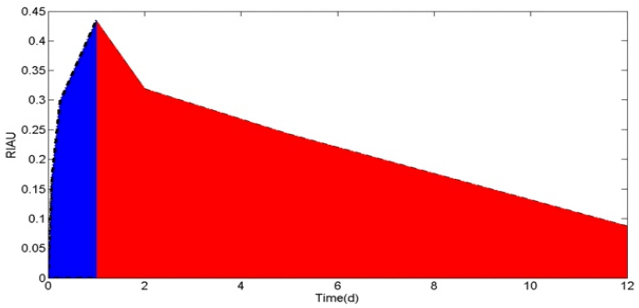

Figure 2. A female patient with $T_{1/2eff}$_S (4.75d)=$T_{1/2eff}$_Q (4.75d). The area under the curve from 1d to infinity was the same with these two methods, for the $T_{1/2eff}$_S=$T_{1/2eff}$_Q. However, the sQMHF ignored the area under the curve during the first day, i.e. blue region, that was included in the SOPD. It is obvious that her RT_S (3.16d)>RT_Q (2.94d).]

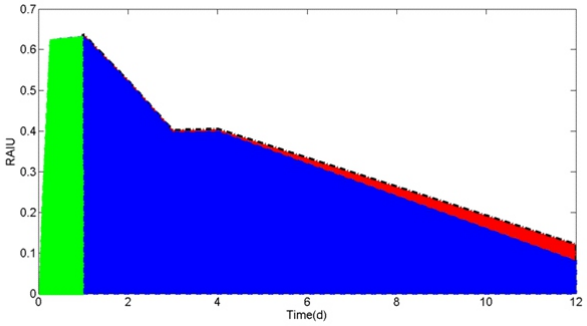

Figure 3. A female patient with $T_{1/2eff}$_S (3.55d)<$T_{1/2eff}$_Q (4.57d). The area under the curve from 1d to infinity calculated by SOPD and sQMHF was presented as blue and (blue+red) region, respectively. The area under the curve during first day was presented as green region. In this case, the area of green region was smaller than the red one, thus her RT_S (3.92d) <RT_Q (4.21d).

The prescribed ^{131}I activity was 402.4±293.4MBq. The therapeutic TD was 89.4±9.4Gy and its variable coefficient (VC) was 0.105. The therapeutic TD was significantly higher than the prescribed TD (75Gy) (t=9.84, P<0.01). The RE of the therapeutic TD (intra-person) was -0.01±0.02, significantly less than the VC (0.105) of therapeutic TD (inter-person) (t=-39.6, P<0.01). However, four patients' therapeutic TD were not larger than 75Gy (listed in the Table 1). Both $T_{1/2eff}$_S<$T_{1/2eff}$_Q and RT_S<RT_Q were the outstanding features of them. For the sample size was too small (n=4) to gain a statistical significant difference neither between $T_{1/2eff}$_Q and $T_{1/2eff}$_S nor between RT_Q and RT_S.

Table 1. *The effect half-life time and residence time in patients whose therapeutic TD≤75Gy*

Num	$T_{1/2eff}$-Q (d)	$T_{1/2eff}$-S (d)	RT-Q (d)	RT-S (d)	Therapeutic TD (Gy)
1	4.57	3.55	4.21	3.92	70.7
2	2.86	1.86	1.68	1.60	72.2
3	4.32	3.97	4.04	4.01	74.4
4	2.98	2.88	2.74	2.69	75.0

Discussion

Iodine-131 is an effective treatment for adult Graves' disease [1-4, 14]; however, the $T_{1/2eff}$ is affected by multi-variable factors and is, therefore, hard to predict [15, 16]. Yet, it is important to measure the exact effect of personal treatment [8, 17, 18]. Up to a point and if we consider hypothyroidism as a goal for treatment, the higher the activity of the ^{131}I absorbed dose administered, the greater the cure rate [2, 3, 19]. Nevertheless, the clinical results sometimes differ from the expected prognosis [20, 21]. One important reason for this difference might be that the therapeutic TD was quite different from the prescribed TD when the prescribed activity of ^{131}I was calculated using clinical formulae (1-5). In this study, we calculated the personal therapeutic TD using the SOPD [8] and demonstrated a significant difference between the therapeutic and prescribed TD; this finding confirmed our hypothesis.

The therapeutic TD was 89.4±9.4Gy, significantly higher than the prescribed TD (t=9.84, P<0.01); 1.19 times that of the prescribed TD. Because the TD is proportion to RT, it is obvious to observe the main reason from Figures 1-3, especially Figure 2. The main reason was that the prescribed TD when calculated using the sQMHF included the absorbed dose accumulated from 1d to infinity and ignored the absorbed dose accumulated during the first day [22]. As a result of this flaw in the sQMHF methodology, the larger absorbed dose accumulated during the first day, the greater the difference between the therapeutic and prescribed TD. Another minor reason for the difference in TD is that the therapeutic TD is affected by the thyroid mass, which is included in formulas (7) and (8) [8], but not in the converted sQMHF (75Gy per 3.7MBq/g). The $T_{1/2eff}$_Q and $T_{1/2eff}$_S was not significantly

different, which was similarity with prior results [11]. However, the little but not significant difference between them may add the variance of RT_Q because of the error propagation rule [23]. As the prescribed ^{131}I activity determined using the sQMHF, the VC of the (inter-personal) therapeutic TD was 0.105 in this study, which may lead to a different result from the anticipated prognosis. If the prescribed ^{131}I activity was determined using converted formula (8) (A=D·M/RT/E formula (9)) [3], the personal therapeutic TD could narrow the RE to -0.01±0.02, gain similar results with reference [24], offer more precision, and improve physicians' predictive ability. For calculation of RT and $T_{1/2eff}$, the same RAIU test times are required; so, we suggest updating the methodology; i.e. the prescribed ^{131}I activity determined using formula (9).

The limitations of this study are: a) The prescribed activity of ^{131}I determined using formula (8) requires more RAIU data than just the corrected 24h RAIU and requires mathematical skill. This will increase the workload of the medical team, which may delay adoption of this type of methodology in clinical practice. Therefore, we designed a software program based on the SOPD to overcome this weakness. Following the software we suggest prompts to input data on thyroid mass, $RAIU_t$, and the prescribed TD, the prescribed ^{131}I activity is output within seconds. Thus, this software may partially ease the burden on the medical team. b) This type of methodology prolongs the last RAIU test and postpones ^{131}I treatment. However, few patients with Graves' disease must be immediately treated with ^{131}I. In our department, if possible, propranolol and methimazole are administered to alleviate the symptoms of hyperthyroidism. Patients discontinue the methimazole for 3-5d [1-3] and undergo the RAIU test. Most patients are able to tolerate this approach to treatment.

In conclusion, if the prescribed ^{131}I dose is determined using the simplified Quimby-Marinelli-Hine formula method (sQMHF), the difference between therapeutic and prescribed thyroid absorbed dose (TD) will be significant, and the variable coefficient of the inter-personal therapeutic TD will be large. This may be an important explanation for the difference between clinical results and the anticipated prognosis of Graves' disease in patients who shall receive ^{131}I therapy. According to formula (8), the personal prescribed ^{131}I dose can be calculated more precisely and the error of (intra-personal) therapeutic TD can be narrowed. Thus, physicians will better predict the prognosis of therapeutic outcome.

Acknowledgement

We are grateful to Natural Science Foundation of China (30800274) and to Natural Science Foundation of Fujian Province (No. 2015J01516, 2016J01611) for funding this study

The authors of this study declare no conflicts of interest

Bibliography

1. Chinese Society of Nuclear Medicine. Guidelines for Graves's disease with hyperthyroidism treated with ^{131}I (2013 version).*Chin J Nucl Med Mol Imaging* 2013; 33: 83-95. (Chinese)
2. Ross DS, Burch HB, Cooper DS et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* 2016; 26: 1343-421.
3. Stokkel MP, Handkiewicz Junak D, Lassmann M et al. EANM procedure guidelines for therapy of benign thyroid disease. *Eur J Nucl Med Mol Imaging* 2010; 37: 2218-28.
4. Leo SD, Lee SY, Braverman LE. Hyperthyroidism. *Lancet* 2016; 388: 906-18.
5. Goldsmith SJ. Endocrine System. In Christrian PE, and Waterstram-Rich KM. *Nuclear Medicine and PET/CT Technology and Techniques.7th edition. Elsevier. St Lousi*, 2012: 444-83.
6. Orsini F, Traino AC, Grosso M et al. Personalization of radioiodine treatment for Graves' disease: a prospective, randomized study with a novel method for calculating the optimal ^{131}I-iodide activity based on target reduction of thyroid mass. Q *J Nucl Med Mol Imaging* 2012; 56: 496-502.
7. Sapienza MT, Coura-Filho GB, Willegaignon J et al. Clinical and dosimetric variables related to outcome after treatment of Graves' disease with 550 and 1110MBq of ^{131}I: results of a prospective randomized trial. *Clin Nucl Med* 2015; 40: 715-9.
8. Hänscheid H, Canzi C, Eschner W et al. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases. *Eur J Nucl Med Mol Imaging* 2013; 40: 1126-34.
9. Chen Y, Xie SP, He F et al. Evaluation of the efficacy of standardized uptake value (SUV)-shape scheme for thyroid volume determination in Graves' disease: A comparison with ultrasonography [J]. *Asia Ocean J Nucl Med Biol* 2017; 5: 44-8.
10. Canzi C, Zito F, Voltini F et al. Verification of the agreement of two dosimetric methods with radioiodine therapy in hyperthyroid patients. *Med Phys* 2006; 33: 2860-7.
11. Willegaignon J, Sapienza MT, Coura Filho GB et al. Determining thyroid ^{131}I effective half-life for the treatment planning of Graves' disease. *Med Phys* 2013; 40: 022502.
12. Hänscheid H, Lassmann M, Reiners C. Dosimetry prior to I-131-therapy of benign thyroid disease. *Z Med Phys* 2011; 21: 250-7.
13. Merrill S, Horowitz J, Traino AC et al. Accuracy and optimal timing of activity measurements in estimating the absorbed dose of radioiodine in the treatment of Graves'disease. *Phys Med Biol* 2011; 56: 557-71.
14. McCready VR. Radioiodine - the success story of Nuclear Medicine: 75th Anniversary of the first use of Iodine-131 in humans. *Eur J Nucl Med Mol Imaging* 2017; 44: 179-82.
15. Hautzel H, Pisar E, Yazdan-Doust N et al. Qualitative and quantitative impact of protective glucocorticoid therapy on the effective ^{131}I half-life in radioiodine therapy for Graves disease. *J Nucl Med* 2010; 51: 1917-22.
16. Pirnat E, Zaletel K, Gaberšček S, Hojker S. The outcome of ^{131}I treatment in Graves' patients pretreated or not with methimazole. *Hell J Nucl Med* 2011; 14: 25-9.
17. Brinks P, Van Gils K, Kranenborg E et al. Measuring the actual I-131 thyroid uptake curve with a collar detector system: a feasibility study. *Eur J Nucl Med Mol Imaging* 2017; 44: 935-40.
18. Willegaignon J, Sapienza MT, Coura Filho GB et al. Determining thyroid ^{131}I effective half-life for the treatment planning of Graves' disease. *Med Phys* 2013; 40: 022502.
19. Esfahani AF, Kakhki VR, Fallahi B et al. Comparative evaluation of two fixed doses of 185 and 370MBq ^{131}I, for the treatment of Graves' disease resistant to antithyroid drugs. *Hell J Nucl Med* 2005; 8: 158-61.
20. Šfiligoj D, Gaberšček S, Mekjavič PJ et al. Factors influencing the success of radioiodine therapy in patients with Graves' disease. *Nucl Med Commun* 2015; 36: 560-5.
21. de Jong JA, Verkooijen HM, Valk GD et al. High failure rates after ^{131}I therapy in Graves hyperthyroidism patients with large thyroid volumes, high iodine uptake, and high iodine turnover. *Clin Nucl Med*

2013; 38: 401-6.
22. Willegaignon J, Sapienza M.T, Coura-Filho G.B et al. Graves' disease radioiodine-therapy: choosing target absorbed doses for therapy planning. *Med Phys* 2014; 41: 012503.
23. Rigas G, Sakellarios A, Bourantas CV et al. Error propagation in the characterization of atheromatic plaque types based on imaging. *Comput Methods Programs Biomed* 2015; 121: 161-74
24. Rink T, Bormuth FJ, Braun S et al. Concept and validation of a simple model of the intrathyroidal iodine kinetics. *Nuklearmedizin* 2004; 43: 21-5.

Emmet Gowin, Artful Genealogies, 1976. From The Gender Equation by Sue V. Rosser. The Sciences, September/October 1992; pages 42-47.