RAPID TURNOVER PATTERN OF RADIOIODINE UPTAKE IN GRAVES' DISEASE: CLINICAL CORRELATION AND THERAPY OUTCOME

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ABSTRACT

The retrospective study was designed to explore the prevalence of rapid turnover pattern (RTP) of radioiodine (^{131}I) uptake in the patient with Graves' disease, to find the possible clinical factors associated with this kind of uptake pattern and to compare the successful rate of ^{131}I treatment between RTP and non-rapid turnover pattern (NRTP). The subjects were Graves' disease patients referred for the first ^{131}I therapy. The 3-hour uptake value > 24-hour uptake value was classified as RTP, whereas 3-hour value < 24-hour value was classified as NRTP. Of all 938 study subjects, 252 cases (26.9%) had RTP. The successful rate of RTP group was significantly lower than that of NRTP group (17.1% versus 42.7%, $p < 0.001$). In univariate analyses, significant associations were found between the RTP and age ($p = 0.021$), prior >24-month antithyroid drug treatment ($p = 0.011$), thyroid gland size, 3-hour and 24-hour uptake values ($p < 0.001$). However, multiple logistic regression analyses showed only 3- and 24-hour uptake values were the independent predictors of RTP ($p < 0.001$). RTP, even found in only about one-fourth of Graves' disease patients, affects the outcome of ^{131}I treatment. No clinical history is reliable to predict the possibility of RTP, except the 3- and 24-hour uptake values.

INTRODUCTION

It has been accepted that treatment of Graves' hyperthyroidism by ^{131}I is a convenient, safe and rather inexpensive method and can effectively control hyperthyroidism with a single dose.[1] A variety of factors have been reported to affect the success of ^{131}I therapy including size of thyroid gland, homogeneity of radioiodine uptake in the thyroid gland, pretreatment with antithyroid drug (ATD) and ^{131}I administered dose regimen.[1-4] The radiation dose to the thyroid gland depends on the amount of administered ^{131}I per gram of thyroid gland weight and the duration of ^{131}I retaining in the gland. About 15% of Graves' disease patients was reported to have the unusual radioiodine uptake called the rapid turnover pattern in which the radioiodine was discharged more rapidly from the gland than usual.[5-7] Radiation dose to the thyroid in this uptake pattern, therefore, is lower than expected resulting in a higher incidence of treatment failure. Moreover, an in-

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creased total body radiation is acquired from the release of protein-bound ^{131}I into the blood circulation.[6]

An easy and practical method in measuring the retaining time of radioiodine in the thyroid gland was the measurement of an early to late radioiodine thyroid uptake ratio proposed by Aktay et al.[5] Generally in Graves' disease, the early uptake value at 3 or 4 hours after oral ^{131}I administration should be lower than the late uptake value at 24 hours or determined as the uptake ratio less than 1. In the patient with rapid turnover pattern of uptake, the uptake ratio was equal or more than 1. The study of Aktay et al. found that besides male gender, prior ATD treatment and non-Graves' hyperthyroidism, the high early uptake value and high uptake ratio were other two additional factors associated with the unfavorable outcome of ^{131}I therapy in hyperthyroid patients, whereas size of thyroid gland, late uptake value and amount of radioiodine dose per gram of thyroid tissue were not significantly associated with the outcome. We thus would like to find the prevalence of Graves' disease with rapid turnover pattern of radioiodine uptake and compare the successful rate of ^{131}I therapy in both rapid and non-rapid turnover uptake groups. Any possible associated clinical factors to predict the rapid turnover uptake pattern was also explored.

MATERIALS AND METHODS

SUBJECTS

We retrospectively studied medical records of consecutive Graves' disease patients residing in the northeast Thailand and referred for the first ^{131}I treatment at the Division of Nuclear Medicine, Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University from June 1994 to August 2000. Clinical diagnosis of Graves' disease, later confirmed by the nuclear medicine physician, was determined by referring physicians and was supported by the elevation of serum thyroxine and/or serum triiodothyronine, with or without serum thyroid stimulating hormone. The exclusion criteria were patients who had history of ^{131}I therapy or had any type of thyroid surgery and received lithium administration before or after ^{131}I uptake and treatment. Data regarding age at the time of ^{131}I treatment, gender, indication for ^{131}I treatment, weight of thyroid gland estimated by palpation, date of ^{131}I treatment, result of ^{131}I thyroid uptake test, date of established euthyroidism and permanent hypothyroidism following ^{131}I therapy and date of the last follow-up were recorded. The last evaluation was at the end of July 2001. This study was approved by the Ethics Committee of the Faculty of Medicine, Khon Kaen University.

^{131}I THYROID UPTAKE TEST AND ^{131}I TREATMENT

In performing radioiodine thyroid uptake test, contraindications of ^{131}I treatment, women during pregnancy and breast-feeding, were firstly excluded before for the test. ATD, if taken, was discontinued at least 7 days before the study. Other drugs and foods known to affect iodine uptake by the thyroid gland were refrained for their appropriate periods of time. At least 4-hour fasting before ^{131}I administration was recommended in all subjects to make sure that radioiodine could be properly absorbed by gastrointestinal tract.

Radioactivity of 20 microCuries (?Ci) of the standard ^{131}I solution, supplied by the Office of Atomic Energy for Peace, Bangkok, Thailand was counted before and after ingestion by the patient, and then radioactivity at 10-cm distance from the patient's neck extended by a pillow under the shoulders was measured at 3 and 24 hours later. Background radioactivity was corrected by measuring radioactivity at 10-cm distance from patient's thigh at the level of 10-cm

above the knee. Time-decay correction was also computed. All radioactivity measurements were performed by the external counter probe system of the Elscint Company, model DTR-4A. Thyroid uptake value was calculated according to the following equation:

$$\% \text{ uptake of } {}^{131}\text{I by the thyroid} = \frac{\text{neck counts - background counts}}{\text{standard counts - background counts}} \times 100$$

In determining the ^{131}I dose for individual patients, 24-hour thyroid uptake value and weight of thyroid gland were used for calculation to achieve 100 ?Ci of ^{131}I per gram of thyroid tissue. A few patients with history of cardiac failure or cardiac arrhythmia were treated with a higher dose regimen of 150 ?Ci per gram. There were two nuclear medicine physicians involving in the ^{131}I treatment during the study period.

ATD and/or beta-blocker were prescribed as needed after ^{131}I treatment to the individual case according to the justification of physician. Although there was no exact follow-up schedule after ^{131}I treatment, each follow-up time was usually between 3 months and one year, mostly according to the severity of hyperthyroidism. Retreatment with ^{131}I was considered in persistent hyperthyroid cases in no shorter than 3 months after the previous dose.

CLASSIFICATION OF THE UPTAKE PATTERN AND THE SUCCESS OF ^{131}I TREATMENT

The rapid turnover pattern of uptake was indirectly classified when the 24-hour uptake value was equal or less than the 3-hour uptake value, otherwise classified as the non-rapid turnover uptake pattern.

In determining the success of ^{131}I therapy, the subjects were classified into one of the three outcomes including success, failure or undetermined. The success was considered at 6 months after treatment with patients having no symptoms and signs of hyperthyroidism even not taking ATD. The failure was defined as the patients still had symptoms and signs of hyperthyroidism at least 6 months after treatment or retreatment with ^{131}I was administered. The undetermined outcome was defined if the follow-up time was less than 6 months and the subjects were not retreated during this time.

DATA HANDLING AND STATISTICAL ANALYSIS

For descriptive analysis of patient's characteristics, continuous variables including age, thyroid gland weight, radioiodine uptake value were reported as mean $\pm$ standard deviation (SD) together with range. Ratio or percentage was used to present categorical variables including gender and indication for ^{131}I therapy. Univariate and multivariate analyses were used to determine that which factors contributed to the prediction of pattern of radioiodine thyroid uptake. The data analysis was performed using STATA, version 6. Statistical significance was defined as $p < 0.05$.

RESULTS

Of all 1,029 Graves' disease patients treated by radioiodine during the time of study, 91 subjects were excluded; 46 cases because of having a previous history of thyroid surgery and 45 cases due to an incomplete data obtained. The rest 938 cases, therefore, were enrolled for analysis. All subjects lived in the province of the northeast Thailand. Characteristics of subjects including age, gender, estimated thyroid gland weight, indication for ^{131}I treatment (new cases without prior ATD treatment, medical failure within 6-month ATD treatment, failure between 6-month and 24-month ATD treatment, failure after 24-month ATD treatment, relapse of hyperthyroidism within 2 years after ATD cessation and

relapse beyond 2 years after ATD cessation), 3-hour and 24-hour thyroid uptake values were shown (Table 1).

Of all 938 subjects, 252 (26.87%) had the uptake of rapid turnover type while the uptake of the remaining 686 (73.13%) were non-rapid turnover. In comparison of the outcome of ^{131}I therapy between the two groups of uptake pattern, 275 subjects –53 cases (19.27%) of rapid turnover group and 222 cases (80.73%) of non-rapid turnover group–were excluded since their treatment outcome was undetermined. The rest 663 cases included 199 (30.00%) and 464 (70.00%) subjects with rapid and non-rapid turnover uptake pattern, respectively. It was found that the successful treatment was significantly lower in the rapid turnover group (34 cases, 17.1%) as compared with that in the non-rapid turnover group (198 cases, 42.7%), $p < 0.001$.

The relevant clinical data of both rapid and non-rapid turnover groups in all subjects enrolled were shown in Table 2. By the univariate analysis, significant association was found between the rapid turnover pattern and the younger age subjects ($p = 0.021$), subjects with pretreatment with ATD for more than 24 months ($p = 0.011$), the larger thyroid gland size ($p < 0.001$), the higher 3-hour ($p < 0.001$) and the lower 24-hour uptake values ($p < 0.001$). However, the multivariate analysis showed that only 3-hour and 24-hour uptake values were the independent predictors of the rapid turnover pattern ($p < 0.001$).

Table 1. Characteristics of subjects. (N = 938)

Characteristic	Value
Gender (female: male)	
Number	751 : 187
Ratio	4 : 1
Age (year)	
mean ± SD	40.8 ± 11.6
range	14 - 75
Thyroid gland (g)	
mean ± SD	44.5 ± 23.6
range	20 - 200
Indications: number (%)	
no previous ATD	19 (2.0%)
ATD < 6 months	144 (15.4%)
ATD 6 > 24 months	278 (29.6%)
ATD >2 years	382 (40.7%)
relapse < 2 years	80 (8.5%)
relapse >2 years	35 (3.7%)
3-hour uptake (%)	
mean ± SD	68.8 ± 20.7
range	11.1 - 98.7
24-hour uptake (%)	
mean ± SD	79.8 ± 11.2
range	33.5 - 98.8

Table 2. Comparative characteristics of subjects with rapid and non-rapid turnover patterns.

Characteristic	Rapid turnover (N = 252)	Non-rapid turnover (N = 686)	Significance
Gender (female: male)			
Number	211 : 41	540 : 146	NS
Ratio	5.2 : 1	3.7 : 1	
Age (year)			
mean ± SD	39.3 ± 11.5	41.4 ± 11.6	p = 0.021
range	16 - 70	14 - 75	
Thyroid gland (g)			
mean ± SD	56.6 ± 27.9	40.1 ± 20.2	p < 0.001
range	20 - 200	20 - 150	
Indications: number (%)			
no previous ATD	1 (0.4%)	18 (2.6%)	NS
ATD < 6 months	37 (14.7%)	107 (15.6%)	NS
ATD 6 > 24 months	76 (30.2%)	202 (29.5%)	MS
ATD >2 years	120 (47.6%)	262 (38.2%)	p = 0.011
relapse < 2 years	14 (5.6%)	66 (9.6%)	NS
relapse >2 years	4 (1.6%)	31 (4.5%)	NS
3-hour uptake (%)			
mean ± SD	86.2 ± 6.9	62.4 ± 20.4	p < 0.001
range	61.6 - 98.7	11.1 - 97.3	
24-hour uptake (%)			
mean ± SD	77.9 ± 9.7	80.6 ± 11.6	p < 0.001
range	45.5 - 96.4	33.5 - 98.8	

DISCUSSION

Calculation of the absorbed radioiodine dose in the thyroid gland is a very important factor in ^{131}I therapy for Graves' disease. It can be performed by measurement of the effective half-life of radioiodine in the gland. However, the effective half-life cannot be practically calculated since repeated measurements of thyroid uptake cannot be done in every patient. Generally, two-day radioiodine thyroid uptake measurements are used to show the pattern of iodine retention in the gland and to calculate the appropriate treatment dose of ^{131}I to Graves' disease patients. Aktay et al. used a 4- to 24-hour ^{131}I uptake ratio as an index of thyroidal ^{131}I retention and proposed it as a practical means to determine the effective half-life without the need for extended thyroid uptake measurements.[5]

The prevalence of rapid turnover pattern of radioiodine uptake has been rarely reported in the literature. This study showed that the prevalence of this kind of uptake pattern, based on the early to late uptake ratio ≥ 1, was about a quarter (26.9%) in our study population. This figure was slightly higher than that found in the study of Aktay et al., which was 15%.[5]

The successful rate of ^{131}I therapy in the rapid turnover pattern group (17.1%) was significantly lower than that in the non-rapid turnover pattern group (42.7%), $p < 0.001$). This finding was in accordance with the study of Aktay et al., which reported 52% and 89% successful rate in the rapid and non-rapid turnover group respectively. Higher failure rate of treatment in the rapid turnover pattern was directly explained as a shorter retention time for ^{131}I to irradiate thyroid gland and consequently less biological damage occurred in the gland. Furthermore, it could give rise to the increased amount of radiolabeled thyroid hormones or protein-bound ^{131}I circulating in the blood and irradiating normal tissue, causing undesirable and probably hazardous radiation exposure to various organs especially the bone marrow.[6]

Although the rapid turnover pattern gives an unfavorable ^{131}I treatment outcome, the effectiveness of treatment can be enhanced by the adjunct treatment with lithium. Its action is by the blockage of organic iodine and thyroid hormone release from the thyroid gland [8], so a longer retention of ^{131}I in the gland can be achieved, resulting in a longer biological effect of radiation to the thyroid. It is beneficial particularly in young patients where the total body radiation dose must be kept to a minimum.[9-10]

To the best of our knowledge, clinical factors possibly associated with the rapid ^{131}I turnover pattern have never been clearly stated. We therefore try to find the clinical variables likely to predict this type of uptake pattern. In univariate analysis, age, history of pretreatment with ATD for more than 24 months, thyroid gland size, 3-hour uptake value and 24-hour uptake value were found to significantly associate with the rapid turnover pattern ($p < 0.05$), whereas sex predilection, no previous ATD treatment and other periods of pretreatment with ATD were not the associated factors. However, by the multivariate analysis only 3-hour and 4-hour thyroid uptake values were found to be the independent variables to predict this type of uptake pattern. This meant that practically the type of uptake pattern could be known only by performing the actual measurement of at least two-day radioiodine uptake.

Another significance addressing the issue about the rapid turnover pattern is about the calculation of late radioiodine uptake by using early uptake value. Some institutes undertook the study to acquire the formula in order to calculate the late 24-hour uptake value by the early 3- to 6-hour uptake value without actual measurement of the late uptake and found that the calculated late uptake value correlated in the moderate to high degrees with the actual measured late uptake value.[11-13] Moreover, it was also showed that the administered doses of ^{131}I derived from the calculated and the actual measured late uptake were very close. By this method, ^{131}I therapy could be completed within one single visit. Morris et al.[14] reported that the prediction of late uptake value by this method might not be used in Graves' disease patients who were likely to have rapid turnover uptake. Eliminating these patients before developing the regression equation to predict the late uptake value yielded an accurate calculation of the predicted late uptake. The authors suggest that the separate regression equations should be acquired from both groups of uptake pattern to get the suitable formula to predict the late uptake value in each specific group of patients.

As with most retrospective studies, this

study had certain shortcomings. Some degree of error regarding the estimation of thyroid gland weight by palpation was expected in particular with the larger gland size. Among the experienced clinicians, the interobserver variability for the estimate of thyroid gland was could be significant. In eliminating this subjectivity of the manual estimation, the use of ultrasonography to measure the thyroid volume was reported to be significantly correlate with the manual estimation by the endocrinologists and was recommended as a safe and precise way to determine the actual thyroid size when calculating the treatment dose.[15-16] Another drawback of this study, since the subjects without pretreatment with ATD in our study population was only 2%, association between presence or absence of ATD pretreatment and the type of turnover pattern was not reliably determined. Berg et al. found that ATD could cause a significantly faster turnover of radioioidine from the gland [6] so it was possible to be another factor associated with the rapid turnover pattern. This issue remains to be determined in further studies.

In conclusion, our study revealed the uncommon but significant proportion of patients with rapid turnover pattern and its negative effect on ^{131}I treatment outcome. Moreover, it was shown that none of the clinical characteristics could be used to predict this kind of uptake pattern.

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