

Original article

The Influence of Antithyroid Drug Discontinuation to the Therapeutic Efficacy of ^{131}I in Hyperthyroidism

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Abstract

The influence of antithyroid drugs (ATDs) on the therapeutic efficacy of radioactive iodine in hyperthyroidism is still controversial. The aim of this study was to evaluate the effect of ATD discontinuation to the therapeutic efficacy of I-131 in hyperthyroidism patients with long-term ATD treatment. Retrospective study was done to 39 subjects with hyperthyroidism who had been treated with doses of 300 MBq radioactive iodine. The subjects were divided into three groups: Group I ($n = 14$) had been using ATDs for more than one year and discontinued more than three days; group II ($n = 14$) had been using ATDs for more than one year but discontinued only for three days or less, and group III ($n = 11$) has never been used any ATD before radioactive iodine treatment. There was a significant difference in the therapeutic efficacy after three months of radioactive iodine treatment between group I and group II ($P = 0.018$), group II and group III ($P = 0.017$), but not between group I and group III ($P = 1.0$). There was no observed difference on the therapeutic efficacy between the three groups at 6 months after radioactive iodine therapy ($P = 0.143$). Administration of ATDs more than 1 year without discontinuation decreased response of radioactive iodine treatment in 3 months follow-up. Discontinuation of ATDs for more than 3 days before radioactive iodine treatment is recommended.

Keywords: Antithyroid drug, hyperthyroidism, radioactive iodine

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism. It is an autoimmune disorder in which thyroid-stimulating hormone receptor antibodies can cause the thyroid gland synthesize large amounts of thyroid hormones. The three treatment modalities are antithyroid drugs (ATDs), radioactive iodine, and thyroidectomy. Radioactive iodine is increasingly used as the treatment of choice in most patients with Graves' hyperthyroidism because of its ease, low cost, and low rate of complications and relapse.^[1,2]

Certain medications and other conditions may influence the result of radioactive iodine therapy

such as ATDs, uncontrolled iodine intake from food or medication, radiographic contrast materials, and amiodarone. Many studies warned that the medications or substances should be stopped before radioactive iodine therapy. Several treatment protocols concerning ATD withdrawal before radioactive iodine therapy have been reported.^[1,3]

The three ATDs that are often used are propylthiouracil (PTU), methimazole (MMI), and carbimazole (CMZ). They are used either as a primary therapy for a certain period of time while awaiting remission of the disease, or as pretreatment prior to radioactive iodine treatment. The emergence of the opinion to provide antithyroid drugs as the treatment of choice is often due to fear of radiation effects. Many patients receive ATD therapy for many years before finally deciding to get radioactive iodine.^[4-7]

The influence of ATDs on the response of radioactive iodine treatment is still controversial. Many studies have shown the correlation between ATD treatment and failure rate of radioactive iodine therapy, but others

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shown no correlation. The Society of Nuclear Medicine in procedure guideline for therapy of thyroid disease with ¹³¹Iodine suggested that ATDs should be discontinued for at least 3 days before the radioactive iodine therapy is given.^[3,6,8,9]

Most of hyperthyroidism patients are referred to our nuclear medicine department receipt oral ATDs before radioactive iodine therapy. The time interval between oral ATDs discontinuation and radioactive iodine therapy was different in each patient. We have no experience in how long is the appropriate time of ATD discontinuation before radioactive iodine therapy.

The aim of this study was to evaluate the effect of ATD discontinuation to the therapeutic efficacy of I-131 in hyperthyroidism patients with long-term ATDs treatment. This study was also to define the optimal time interval between ATD discontinuation and radioactive iodine therapy.

Materials and Methods

Subjects

The institutional ethical committee approved the study. Subjects were patients with hyperthyroidism who were treated with radioactive iodine at our nuclear medicine department from January 2010 to December 2011. Inclusion criteria were as follows: Hyperthyroidism patients 14 years and older who received 300 MBq of radioactive iodine, treated or untreated with ATDs for one year or more, no history of smoking, diffuse goiter, and complete of medical record data for 6 months of monitoring.

Methods

Subjects were divided into three groups: Group I ($n = 14$) were subjects that ATDs discontinued more than three days; group II ($n = 14$) were subjects who discontinued ATDs only for three days or less, and group III ($n = 11$) was never used any ATD before radioactive iodine therapy (control group). Baseline evaluation included evaluation of thyroid scintigraphy, thyroid hormone (T3 and free T4) and thyroid-stimulating hormone sensitive (TSHs) on the day of radioactive iodine administration. T3, free T4 (FT4), and TSHs serum level were measured 2 times in 6 months after ¹³¹I treatment. Subjects were considered to be cured when they developed euthyroidism or permanent hypothyroidism. Euthyroidism was defined as T3, FT4, and TSHs serum levels within the normal range. Hypothyroidism was defined as low thyroid hormone and increased TSHs. Cured rates were observed 3 and 6 months after radioactive iodine.

Statistical analysis

Baseline subjects characteristic were expressed as mean \pm SD for quantitative variables and ratio for qualitative variables. The baseline characteristics of the three groups were compared by nonparametric Mann-Whitney test or analysis of variance (ANOVA) for quantitative variables, respectively. Differences of cure rate between the three groups (Group I and II, II and III, I and III) at 3 months and 6 months were compared with the Chi-square and Fisher's exact test.

Result

A total of 39 subjects (8 men and 31 women) were included in this study. Subjects' characteristics in each group are shown in Table 1.

Prior to I-131 treatment, the characteristics of the three groups did not differ with regard to age and gender ($P = 0,629$; $P = 0,104$) but differ to FT4 value ($P = 0,013$). Free T4 in group I and III were higher than group II. There were no significant difference between group I and group II in duration of disease ($P = 0,227$).

In the 3 month follow-up after radioactive iodine therapy, 8 subjects (57%) of group I, 2 subjects (14%) of group II, and 7 subjects (64%) of group III showed a good response. Six subjects (43%) of group I, 12 subjects (86%) of group II, and 4 subjects (36%) of group III Showed less response. Six months after treatment 11 subjects (79%) of group I, 8 subjects (57%) of group II, and 10 subjects (90%) of group III showed a good response. Only 3 subjects (21%) of group I, 6 subjects (43%) of group II, and 1 subjects (10%) of group III were required to repeat radioactive iodine therapy [Table 2].

There was a significant difference between the group I and the group II ($P = 0.018$), group II and group III ($P = 0.017$), but no significant difference between group I and group III ($P = 1.0$) three months after radioactive iodine therapy. There was no difference in the cure rate was observed between group I and the group II ($P = 0.419$), group II and group III ($P = 0.09$), and group I and

Table 1: Subjects characteristic

Parameter	Group I	Group II	Group III
Number of subjects	14	14	11
Gender (male/female)	4/10	2/12	2/9
Age (mean \pm SD) (range)	38,9 \pm 11,3 (20-54)	44,7 \pm 10,2 (29-59)	34,7 \pm 13,1 (19-60)
ft4 (mean \pm SD)	5,8 \pm 3,87	2,77 \pm 1,96	4,53 \pm 1,80
Duration of disease (months) (mean \pm SD)	50,14 \pm 40,16	69 \pm 31,79	4 \pm 2,89

SD: Standard deviation; FT4: Free thyroxine

group III ($P = 0.604$) at 6 months after radioactive iodine therapy [Figure 1].

Discussion

The effect of oral ATDs on radioactive iodine therapy had been studied for a long time, but it is still controversial. The results of this study showed that radioactive iodine therapy provided maximum results in subjects who had not received ATDs prior to radioactive iodine therapy or in subjects who have stopped ATDs for more than 3 days prior to radioactive iodine therapy. This indicates that the effectiveness of radioactive iodine therapy in hyperthyroidism patients taking ATDs for more than 1 year can be improved by discontinuation of ATDs more than 3 days.^[10,11]

Some studies suggested that the ATDs may have a protective effect, which leads to lowering the effective half-life and uptake of radioactive iodine in the thyroid gland. Thus, the target organ (thyroid) dose will decrease, resulting in a decrease of the effectiveness of radioactive iodine therapy. Moka *et al.* said that discontinuation of ATDs before radioactive iodine is needed. This study is supported by Hancock *et al.*, Andrade *et al.* and Walter *et al.*, which advocated termination ATDs one week prior to radioactive iodine therapy.^[3,12-14]

Tuttle *et al.* compared hyperthyroidism patients with and without PTU treatment prior to radioactive iodine therapy. They concluded that the use of PTU influenced

the success of radioactive iodine therapy, although PTU was stopped for approximately 4 days. They also said that in these conditions, the success of therapy can still be improved by increasing the dose of radioactive iodine. In this study, the therapeutic dose of ^{131}I was uniform to avoid bias, which may occur and influence the results of this study.^[15] We used 300 MBq of radioactive iodine based on our empirical experience for fixed low dose, with the consideration that average body weight of people of Indonesians less than Europeans or Americans. Several studies that compared efficacy of different doses of radioactive iodine included doses of 200 MBq, 259 MBq, less than 370 MBq, or greater than 370 MBq were done.^[16-18]

Imseis *et al.* evaluated the influence of PTU and MMI to therapeutic efficacy of ^{131}I in hyperthyroidism that pretreated with. The study concluded that the cure rate of ^{131}I therapy was significantly reduced after pretreatment with PTU, even when it was discontinued for 5-55 days before radioactive iodine therapy. Similar premedication with MMI did not interfere the response to ^{131}I therapy.^[19] This study was supported by Andrade *et al.*, which showed that there was no difference after radioactive iodine treatment with or without MMI pretreated. Shivaprasad *et al.* (2015) concluded that patients pretreated with CMZ have lower efficacy with ^{131}I therapy compared to nonpretreated patients. This study did not analyze separately for each ATD in the baseline, therefore it could not identify the difference of therapeutic efficacy of ^{131}I after pretreatment by each ATD. This study also was not include the goitre size and thyroid uptake, which could potentially cause heterogeneity in the baseline of this study.^[19-21]

Table 2: Cure rates in 3 and 6 months after radioactive iodine therapy

Group	Follow up 3 months				Follow up 6 months				Total
	Cured %		Treated %		Cured %		Treated %		
	2 nd therapy		3 rd therapy		2 nd therapy		3 rd therapy		
I	8	57	6	43	11	79	3	21	14
II	2	14	12	86	8	57	6	43	14
III	7	64	4	36	10	90	1	10	11

Conclusion

The administration of oral ATDs more than one year without withdrawal more than 3 days decreased response of radioactive iodine therapy in the 3 months

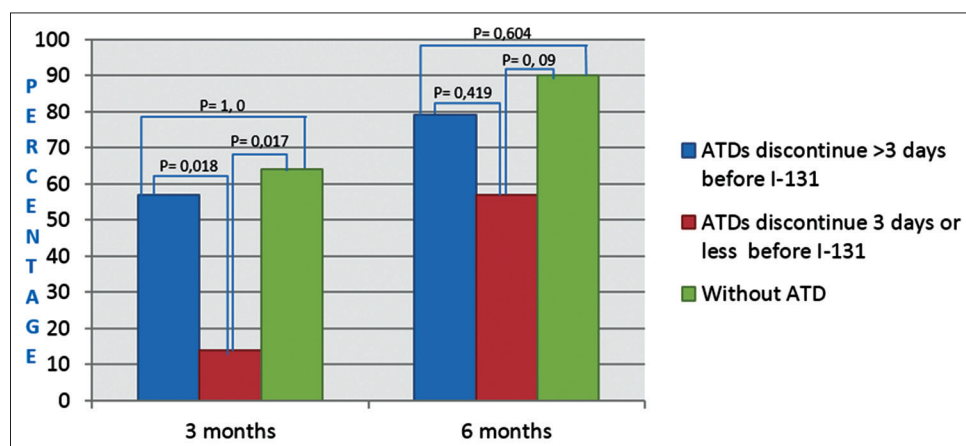


Figure 1: The outcomes of radioactive iodine therapy in percentage and P value

follow-up. A study with a larger number of subjects, separately for each ATD pretreatment, and more attention to confounding factors such as goitre size and thyroid uptake is recommended.

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