

# The Influence of Anti-thyroid Drug Discontinuation to the Therapeutic Efficacy of $^{131}\text{I}$ in Hyperthyroidism

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## Abstract

**Background:** The influence of anti-thyroid 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 ATDs discontinuation to the therapeutic efficacy of  $^{131}\text{I}$  in hyperthyroidism patients with long-term ATD treatment.

**Subject and methods:** Retrospective study was done to 39 subjects with hyperthyroidism who had been treated by the dose 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 the group III (n=11) has never been used any ATD before radioactive iodine treatment.

**Results:** There was a significant difference in the therapeutic efficacy after three months of radioactive iodine treatment between the group I and group II ( $p=0.018$ ), the group II and group III ( $p=0.017$ ) but not between the group I and group III ( $p=1.0$ ). There was no difference in the therapeutic efficacy observed between three groups at six months after radioactive iodine therapy ( $p=0.143$ ).

**Conclusion:** Administration of ATDs more than one year without discontinuation decreased the response of radioactive iodine treatment in three months follow-up. Discontinuation of ATDs for more than three days before radioactive iodine treatment is recommended.

**Keywords:** Anti-thyroid drug, radioactive iodine, hyperthyroidism.

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## 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 to synthesize large amounts of thyroid hormones. The three treatment modalities are

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.<sup>[1,2]</sup>

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.<sup>[1,3]</sup>

Three ATDs that are often used are propylthiouracil (PTU), methimazole (MMI) and carbimazole (CMZ). They are used either as a primary therapy for 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 anti-thyroid drugs as the treatment of choice is often due to fear of radiation effects. Many patients get ATD therapy for many years before finally deciding to get radioactive iodine.<sup>[4,5,6,7]</sup>

The influence of ATDs on the response of radioactive iodine treatment is still controversial. Many studies have shown the correlation between anti-thyroid drugs treatment and failure rate of radioactive iodine therapy, but others show no correlation. Society of Nuclear Medicine in procedure guideline for therapy of thyroid disease with <sup>131</sup>Iodine suggested that the ATD should be discontinued for at least 3 days before the radioactive iodine therapy is given.<sup>[3,6,8,9]</sup>

Most of hyperthyroidism patients refer to our nuclear medicine department to receive oral anti-thyroid drugs before radioactive iodine therapy. The time interval between oral anti-thyroid drugs discontinuation and radioactive iodine therapy was different in each patient. We have no experience how long 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

ATD treatment. This study was also to define the optimal time interval between anti-thyroid drug discontinuation and radioactive iodine therapy.

## **Material and Methods**

### **Subjects**

The study approved by the institutional ethical committee. Subjects were patients with hyperthyroidism who treated with radioactive iodine at our nuclear medicine department from January 2010 to December 2011. Inclusion criteria were as follows: hyperthyroidism patients, 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. Hyperthyroidism patients age more than 14 year.

### **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 discontinued 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 two times in 6 months after <sup>131</sup>I treatment. Subjects were considered to be cured when they developed euthyroidism or permanent hypothyroidism. Euthyroidism was defined as T3, fT4, and TSHs serum level within the normal range. Hypothyroidism was defined as low thyroid hormone and increased TSHs. Cured rates were observed in 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 ANOVA for quantitative variables, as 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 chi-square and the Fisher Exact test.

## Result

A total of 39 subjects (8 men and 31 women) were included in this study.

### Subjects characteristic in each group are shown in Table 1.

Prior to I-131 treatment, the characteristics of 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 3 months follow up after radioactive iodine therapy, 8 subjects (57%) of group I showed a good response, 2 subjects (14%) of group II, and 7 subjects (64%) of group III. Six subjects (43%) of group I, 12 subjects (86%) of group II, and 4 subjects (36%) of group III less response. Six months after treatment showed a good response in 11 subjects (79%) of group I, 8 subjects (57%) of group II, 10 subjects (90%) of group III. Only 3 subjects (21%) of group I, 6 subjects (43%) of group II, and 1 subjects (10%) of group III were required and repeat radioactive iodine therapy [Table 2].

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 ( $p=1.0$ ) in three months after radioactive iodine therapy. There was no difference in cure rate was observed between the group I and the group II ( $p=0.419$ ), group II and group III ( $p=0.09$ ), between group I and 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 until now it is still controversial. The results of this study showed that radioactive iodine therapy provide maximum results in subjects who had not received anti-thyroid drugs prior to radioactive iodine therapy or in subjects who have stopped anti-thyroid drugs for more than 3 days prior to radioactive iodine therapy. This indicates that the effectiveness of radioactive iodine therapy in hyperthyroidism patients taking ATDs more than 1 year can be improved by discontinuation of ATDs more than 3 days.<sup>[10, 11]</sup>

Some studies suggested that the ATDs may have protective effect which lead to lowering the effective half-life and uptake of radioactive iodine in thyroid gland. Thus, the target organ (thyroid) dose will decrease and result in a decrease of the effectiveness of radioactive iodine therapy. Mokaet *al.* said that discontinuation of ATDs before radioactive iodine is needed. This study supported by studies of Hancock *al.*, meta-analysis study by Andrade *al.* and Walter *al.*, which advocated termination of ATDs one week prior to radioactive iodine therapy<sup>[3, 12, 13, 14]</sup>

Study by Tuttle *et al.*, was done to compare hyperthyroidism patients with and without propylthiouracil (PTU) treatment prior to radioactive iodine therapy. They concluded that the use of PTU influenced the successful

of radioactive iodine therapy, although PTU was stopped approximately for 4 days. They also said that in these conditions, the successful of therapy can still be improved by increasing the dose of radioactive iodine. In this study, the therapeutic dose of  $^{131}\text{I}$  was uniform to avoid bias which may occur and influence the results of this study.<sup>[15]</sup> We used 300 MBq of radioactive iodine based on our empirical experience for fixed low dose and consideration that average body weight of people in our country less than European or American. Several studies that compared efficacy of differences dose of radioactive iodine included 200 MBq, 259 MBq, less than 370 MBq, or greater than 370 MBq were done.<sup>[16, 17, 18]</sup>

The study was done by Imseiset *al.* to evaluate the influence of propylthiouracil (PTU) and methimazole (MMI) to therapeutic efficacy of  $^{131}\text{I}$  in hyperthyroidism that pretreated with. The study concluded that the cure rate of  $^{131}\text{I}$  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  $^{131}\text{I}$  therapy.<sup>[19]</sup> This study was supported by Andrade *et al.* which shown that there was no difference after radioactive iodine treatment with or without MMI pretreated. Different study from Shivaprasad *et al.* (2015) concluded that pretreated with Carbimazole (CMZ) have lower efficacy with  $^{131}\text{I}$  therapy compared to nonpretreated patients. This study did not analyzed separately for each ATD in the baseline, therefore it could not identify the difference of therapeutic efficacy of  $^{131}\text{I}$  after pretreatment by each ATD. This study also was not include the goitre size and thyroid uptake which could be potential for heterogeneity in the baseline of this study.<sup>[19, 20, 21]</sup>

## Conclusion

Administration of oral anti-thyroid drugs (ATDs) more than one year without withdrawal more than three days decreased response of radioactive iodine therapy in 3 months following up. 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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**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

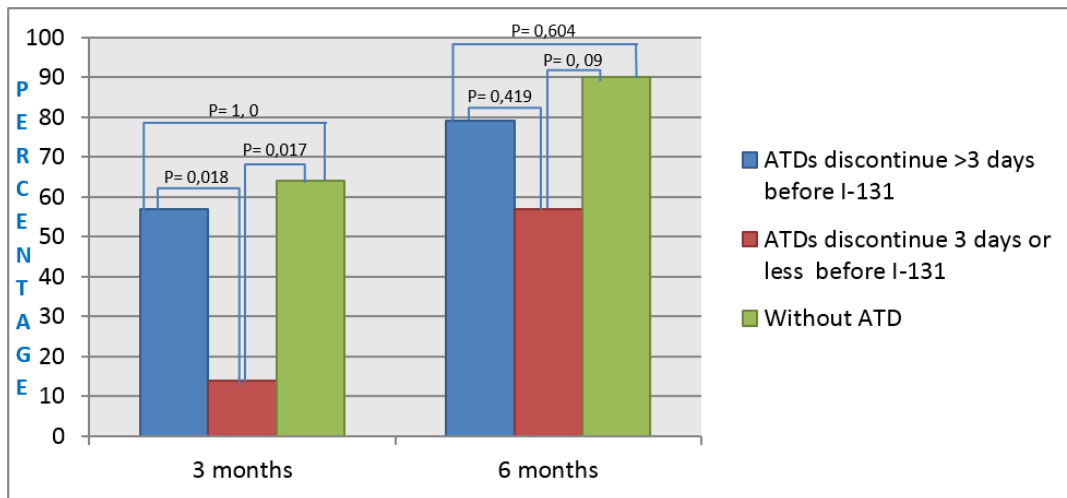
SD: Standard deviation; fT4: free thyroxine  
Original table

**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 2 <sup>nd</sup> therapy	%	Cured	%	Treated 3 <sup>rd</sup> 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

Original

1 table



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

Original figure