ORIGINAL ARTICLE

Effect of pre-treatment with carbimazole on the outcome of radioactive iodine-131 therapy for patients with hyperthyroidism

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Article Information

Total number of
Words 1481
Tables 2

Authors have no conflicts of interest to declare

Keywords: Hyperthyroidism, Graves' Disease, Toxic Multi Nodular Goiter, Radioactive Iodine, Carbimazole

Date of submission: 2020-02-11
Date of acceptance: 2020-07-28

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DOI: http://doi.org/10.4038/cjms.v57i1.4965

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Abstract

Background

The outcome of radioactive iodine therapy with I-131 (RAI) therapy is influenced by many factors. Pretreatment with antithyroid drugs (ATD) is considered as one of the factors affecting the outcome. Carbimazole and methimazole are shown to be having lesser effect on outcome of RAI therapy compared to propylthiouracil.

Objective

This study was aimed to identify the difference in the pre-treatment carbimazole dose and duration among patients with various outcomes after radioiodine therapy for hyperthyroidism.

Methodology

Fifty hyperthyroid patients consented for the study after receiving 10 mCi RAI and they were followed up to monitor the clinical outcome at Nuclear Medicine Unit, Peradeniya. Therapeutic outcome was assessed at 03 and 06 months after RAI therapy by clinical assessment and biochemical thyroid function tests (free thyroxine (fT4) and TSH levels). The data were analyzed using SPSS version 25.

Results

Graves' disease was high (70%) among participants compared to toxic multinodular goiter (30%). Six months after RAI therapy, 84% of the patients responded to the treatment and 16% had persistent hyperthyroidism. The mean daily dose (P=0.193) and mean duration (P=0.563) of carbimazole treatment between these two outcomes didn't show a signigficant difference.

Conclusion

Pretreatment carbimazole dose or the duration do not affect on the outcome of 10 mCi fixed dose RAI therapy for hyperthyroidism.

Background

The common etiologies of hyperthyroidism are Graves' disease (GD), toxic multinodular goiter (TMNG) and autonomous toxic nodule (ATN) (1). Antithyroid drugs, radioactive iodine therapy with I-131 (RAI) and surgery are the main treatment options; the latter two being the definitive treatments. The commonly used anti-thyroid drugs (ATDs) are methimazole, its precursor carbimazole and propylthiouracil. RAI is a widely used therapeutic radionuclide, produced in a nuclear reactor and its therapeutic effect is obtained by the emission of β radiation [1].

Hyperthyroid patients are usually pretreated with ATDs to reduce the risk of thyroid storm after RAI therapy. Studies have shown that pretreatment ATDs adversely

affects RAI therapy outcome [2]. This has become a challenge regarding the patient selection for ATDs, choice of antithyroid agent, duration of use and adequate dosage [2, 3]. The therapeutic failure after RAI therapy has been high among patients pretreated with propylthiouracil compared to carbimazole or methimazole [4]. This study aims to identify the difference in the pre-treatment carbimazole dose and duration within the various outcomes of radioiodine therapy among hyperthyroid patients.

Methods

Subjects

Hyperthyroid patients, who were referred for RAI therapy to the Nuclear Medicine Unit (NMU), Faculty of Medicine, University of Peradeniya during the period of January 2018 to June 2019 were recruited in the study. A total of 80 patients received RAI-131 therapy during this period and, of them 50 patients who received pretreatment carbimazole consented for the study and follow up.

All study patients had either GD or TMNG. Patho-physiology of thyrotoxicosis was confirmed by ^{99m}Tc thyroid scintigraphy and uptake studies. Relapsing GD, resistance or allergy to ATD or being unfit for surgery were the main indications for the referrals to consider RAI therapy. Patients were asked to stop ATD at least 07 days prior to the RAI administration.

Treatment and follow up

Those patients who received a fixed dose RAI of 10 mCi (370 MBq) on an outpatient basis were referred back to their referring clinicians for routine follow up with special advice on radiation protection measures.

Data related to the clinical diagnosis, free T4 (FT4), TSH values on diagnosis, carbimazole dose and duration were documented on a clinical checklist at the first visit. Clinical thyroid status, thyroid related treatment/ intervention was recorded during each follow up visit and the values of FT4 and TSH after 03 and 06 months from RAI therapy were obtained from the patient's record, for the study purpose.

NMU reference values for FT4 was 9.9-24.3 pmol/L (0.8ng/dl-1.9ng/dl) and 0.25-4.2 mU/L for TSH. The outcome of RAI therapy was categorized as euthyroid, hypothyroid or persistent hyperthyroid at 03 months and 06 months after RAI therapy. Euthyroidism was defined as FT4 and TSH levels within the normal reference range and off from antithyroid drugs and thyroxine replacement. Hypothyroidism was defined as elevated level of TSH above the upper limit of the reference range and low level of FT4 below the lower margin of the reference range and being started on thyroxine replacement. Persistent hyper-thyroidism was defined as elevated FT4 level above the upper margin of the reference range and suppressed TSH level and ongoing treatment with antithyroid drugs or administration of repeated dose of radioiodine.

Patients with euthyroid or hypothyroid status after RAI were considered as therapeutic success while patients with persistent hyperthyroidism at 6 months were considered as therapeutic failure.

Ethical Consideration

Ethical clearance was granted by the Ethics Review Committee, Faculty of Medicine, University of Peradeniya.

Statistical Analysis

Independent sample t-test and One-way ANOVA tests were used to compare the mean carbimazole dose and mean duration of carbimazole treatment between the outcomes of radioiodine therapy. Results were considered statistically significant at $P < 0.05$. The statistical analysis was done using the SPSS version 25.

Results

The study population included 40% (n=20) of males and 60% (n=30) of females with mean ages of 57.5 years and 48.23 years respectively. Seventy percent of the participants had GD (38% females and 32% males) and 30% had TMNG (22% females and 8% males).

Following the RAI therapy, 50% of the participants were euthyroid at three months and 10% of them became hypothyroid by six months. 28% of patients were hyperthyroid at three months and 12% of them became hypothyroid after six months. There were 22% of hypothyroid patients at three months and it increased to 44% by six months (Table 1). A total of 84% of patients had responded to the radioiodine therapy at the end of six months and 16% had persistent hyperthyroidism.

The daily mean pre-treatment carbimazole dose was 31.7 mg/day within the total study population. The mean daily dose of carbimazole before RAI were not different between hypothyroid, euthyroid and hyperthyroid patients at 3 and 6 months after RAI (Table 1).

Six months after RAI therapy, 84% of the study population showed therapeutic success and 16% showed persistent hyperthyroidism. The mean daily dose of carbimazole among these two groups were not significantly different (Table 2).

The mean duration of carbimazole treatment was 49.71 months (52.95 months in males and 47.39 months in females) within the study population. There was no statistically significant difference in the mean duration of

Table 1. Outcomes of radioiodine therapy at 3 and 6 months post treatment and comparison of pre-RAI antithyroid drug dose and duration (N=50)

	3 months				6 months			
Thyroid status	**Hypothyroid**	**Euthyroid**	**Hyperthyroid**	**F-value**	**Hypothyroid**	**Euthyroid**	**Hyperthyroid**	**F-value**
Number of patients (%)	11 (22)	25 (50)	14 (28)		22 (44)	20 (40)	8 (16)	F=0.84,
Pre-RAI mean carbimazole dose (SD) in mg/day	25.9 (17.0)	32.4 (14.2)	35.0 (18.7)	F=1.02, (p=0.37)	29.5 (16.4)	32.5 (16.4)	38.1 (13.8)	F=0.84 (p=0.44)
Pre-RAI mean duration of carbimazole therapy (SD) in months	48.6 (31.1)	53.2 (42.0)	44.3 (36.6)	F=0.23, (p=0.80)	48.8 (35.3)	53.5 (41.5)	41.7 (38.0)	F=0.25m (p=0.78)

Table 2. Comparison of pre-RAI carbimazole dose and duration in patients who succeeded and failed after 6 months of post RAI treatment

	Responders	**Treatment failures**	**P value**
Number (%)	42 (84)	8 (16)	-
Mean carbimazole dose before RAI (SD), mg/day	30.5	38.1	0.19
Mean duration of carbimazole therapy before RAI (SD) in months	51.1	41.7	0.56

carbimazole pre-treatment between patients euthyroid, hypothyroid or persistent hyperthyroid after three or six months (Table 1). The mean duration of carbimazole treatment was not different between the patients who had therapeutic success (euthyroid/hypothyroid) and persistent hyper-thyroidism after 06 months from RAI therapy. (Table 2).

Discussion

The dose or duration of carbimazole therapy before RAI were not different among patients with different treatment outcomes after RAI.

All the subjects in the study received a fixed dose of 10 mCi (370 mCi) RAI. There were 84% of therapeutically successful (hypothyroid or euthyroid) patients after 06 months from RAI therapy and this outcome is comparable with previous studies. More than 80% cure rate has been achieved among patients pretreated with carbimazole, while using a fixed dose of RAI ranging from 350 MBq to 670 MBq in several studies [5-9].

The effect of ATD pre-treatment on the RAI therapy outcome has been studied in several studies. There have been contrasting findings regarding the effect of ATD on the RAI therapy outcome between these studies. Few studies [10-12] have shown that ATD attenuates the outcome of the RAI therapy while certain other studies [7-8, 13-15] oppose these findings. However, simultaneous use of ATDs with RAI therapy have shown higher therapeutic failure rate [7, 16-18] compared to RAI therapy alone. In this present study, carbimazole was discontinued for 07 days prior to the RAI therapy and many other studies which had similar outcome as in this study discontinued carbimazole at least for 3-5 days before RAI therapy [16].

Pre-treatment with methimazole or carbimazole have shown no effect on the outcome of radioiodine therapy and high failure rate has been demonstrated with propylthiouracil even if it is discontinued 4-7 days before RAI treatment [5, 19]. The attenuating effect of ATDs on RAI therapy is explained by many mechanisms. The radioprotective effect of ATD interfere with the RAI therapy efficacy and this has been demonstrated to be higher with propylthiouracil

compared to methimazole or carbimazole. This is mainly due to the presence of sulfhydryl group in propylthiouracil, which is absent in carbimazole [20].

The influence of the pre-treatment duration on the outcome of RAI therapy has not been studied extensively. Few studies have identified that pre-treatment with carbimazole for more than 23.1 months can affect the RAI therapy outcome [5]. However, our patient cohort were pre-treated over a mean duration of 49.7 months but it has not affected the RAI therapy outcome.

Antithyroid drugs are used primarily to achieve euthyroid status among the newly diagnosed patients with severe disease. This helps to maintain the thyroxine levels during the RAI therapy and prevents thyroid storm [10]. Therefore, methimazole or carbimazole is preferred if RAI therapy is being planned. But simultaneous use of methimazole or carbimazole with RAI can increase the failure rate by 5 fold. The failure rate has been significantly high, with small activities of RAI (< 5 mCi) and this can be overcome by increasing the administered activity of RAI [2].

These findings should be interpreted with caution due to several limitations. Firstly, our sample was relatively small, limited to 50 in total. Secondly, we did not specifically determine the treatment adherence. Thirdly, the follow up was limited to six months. However, findings of this study add to the existing literature, addresses a clinically relevant question and provides baseline for further research.

Conclusion

Among patients with hyperthyroidism, pre-RAI carbimazole dose or duration are not significantly different between responders and treatment failures to 10 mCi fixed dose RAI. Future prospective studies with larger study populations and longer durations of follow up are needed to confirm our findings.

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