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RESEARCH ARTICLE

Nuclear medicine

Comparison of radioactive iodine therapy outcome and the duration of pretreatment discontinuation of carbimazole among hyperthyroid patients: a prospective study

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Abstract: The outcome of radioactive iodine (^{131}I) treatment among hyperthyroid patients can be affected by pretreatment with antithyroid drugs (ATD) and they should be discontinued before ^{131}I treatment. This study aims to compare the outcome of ^{131}I treatment among hyperthyroid patients who were off carbimazole for 3–7 days and 8–30 days before the ^{131}I treatment. This prospective cohort study was carried out among 89 hyperthyroid patients referred for ^{131}I treatment at the Nuclear Medicine Unit, Peradeniya (NMU) during August 2018 to February 2020. All these patients received a fixed activity of 10 mCi ^{131}I. Each patient was followed up at a three-month interval for 06 months. The data were collected by directly interviewing the patients, from the clinical records and from the NMU database. Six months after ^{131}I treatment among Graves' disease (GD) patients, 17.9 % had euthyroidism, 59.7 % had hypothyroidism and 22.4 % had hyperthyroidism. The therapeutic success was 77.6 % among them. Of the Toxic Multi Nodular Goitre (TMNG) patients, 36.4 % had euthyroidism, 31.8 % had hypothyroidism and 31.8 % had hyperthyroidism. The overall therapeutic success was 68.2 % among them. Carbimazole discontinuation for 3–7 days and 8–30 days did not show a statistical difference with the ^{131}I treatment outcomes in both GD (Chi-square value = 0.264, p value = 0.876) and TMNG (Chi-square value = 1.743, p value = 0.418). The minimum carbimazole off days among GD was 5 days and 3 days for the TMNG patients. Withholding carbimazole for more than 7 days (8–30 days) before ^{131}I treatment did not influence the therapeutic outcome and discontinuation of carbimazole can be decided on individual basis depending on the comorbid conditions.

Keywords: Carbimazole, hyperthyroidism, radioactive iodine.

INTRODUCTION

Radioactive iodine (^{131}I) is considered as one of the first line treatment in the management of hyperthyroidism (Clarke, 1991). The safety and the effectiveness of ^{131}I have been proven by several long-term follow up studies (Bonnema & Hegedüs, 2012).

Antithyroid drugs (ATD) control the severity and the symptoms of disease in the management of hyperthyroidism. Hyperthyroid patients are brought to euthyroidism or near euthyroidism before ^{131}I treatment to prevent thyroid storm and exacerbation of toxic symptoms after ^{131}I therapy. However, several prospective and retrospective studies have shown that pretreatment with ATD has a negative effect on the final outcome of ^{131}I therapy (Cooper, 2003). This has made the management of primary hyperthyroidism a challenge. Several retrospective studies have assessed the effect of ATD on the outcome of ^{131}I therapy, while only a smaller number of prospective studies have evaluated the effect of ATD on ^{131}I. Studies have shown that ATD reduce the efficacy of ^{131}I therapy (Marcocci *et al*., 1990; Andrade *et al*., 2001.; Braga *et al.*, 2002) and this is high among patients pretreated with propylthiouracil compared to methimazole or carbimazole (Hancock *et al*., 1997; Imseis *et al.*, 1998; Braga *et al*., 2002).

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To minimize the effect of ATD on the ^{131}I treatment, it is suggested to withdraw ATD prior to the ^{131}I administration. Current recommendations and guidelines on this are solely based on single trials and narrative reviews (Walter *et al.*, 2007). The newer recommendation is to withdraw the ATD 3-7 days before the ^{131}I administration to increase the efficacy of ^{131}I therapy (Andrade *et al*., 2001; Bonnema *et al.*, 2002; Eschmann *et al*., 2006; Walter *et al*., 2006). Challenging these recommendations, certain studies have suggested to stop the antithyroid drugs more than 7 days before radioactive iodine administration (Lewis *et al.*, 2013; Prasanna Kumar and Shivaprasad, 2015). But discontinuing the antithyroid drugs for seven days or less has shown a benefit with large dose ^{131}I therapy. But with low dose ^{131}I treatment, the discontinuation required more than seven days (Walter *et al.*, 2009).

The aim of this study was to compare the outcome of radioactive iodine treatment among hyperthyroid patients who were off carbimazole for 3–7 days and 8–30 days before the 10 mCi radioactive iodine treatment.

MATERIALS AND METHODS

Study subjects

This prospective cohort study was carried out among 89 hyperthyroid patients who received radioactive iodine treatment at the Nuclear Medicine Unit (NMU), Faculty of Medicine, University of Peradeniya from August 2018 to February 2020.

Hyperthyroid patients attending the thyroid clinic at the NMU during the study period and who received 10 mCi ^{131}I therapy were accommodated in the study. Initial diagnosis of hyperthyroidism was made by the referring clinicians based on clinical examination and biochemical assessment. All these patients had been pre-treated with carbimazole and were receiving the first dose of ^{131}I. The common indications for requesting ^{131}I treatment were poor response to ATD or reactions to ATD, and unfitness for or refusal of surgery. Routinely, GD and TMNG patients are treated with ^{131}I on an outpatient basis at the NMU. Solitary toxic nodules (STN) patients are not treated with ^{131}I at the NMU, as they require a larger dose of ^{131}I which needs to be treated inward.

Patient preparation and administration of ^{131}I therapy

Once the NMU accepted the patients for radioactive iodine therapy, thyroid function tests were repeated and thyroid uptake studies were done to confirm the diagnosis and the aetiology of thyrotoxicosis. Patients who were on ATD were advised to discontinue antithyroid drugs for at least 1 wk prior to the isotope scan and uptake measurement. Those who were on beta-blockers for symptomatic relief was advised to continue the drug, as beta-blockers do not affect the ^{131}I treatment. If needed, they were asked to continue before and after ^{131}I treatment until they get rid of toxic symptoms.

All hyperthyroid patients underwent ^{99m}Tc-pertechnetate thyroid scan and uptake studies before ^{131}I therapy. Thyroid images were obtained using the MEDISO dual-head SPECT Gamma Camera fitted with a low energy high-resolution parallel hole collimator. Thyroid uptake was calculated by computer software using the image-based pre-injection and post-injection counts and the thyroid image. If the thyroid gland exhibited adequate tracer uptake, the decision to give radioactive iodine therapy was taken by the Nuclear Medicine Physician.

A fixed activity of 10 mCi (370 MBq) of ^{131}I was given under the supervision of a Nuclear Medicine Physician and these patients were referred back to the referring physician. The referring clinicians were requested not to restart ATD for at least 6 wks after the radioactive iodine therapy, and to perform the initial TSH and FT4 tests after 6 wks. All ^{131}I administered patients were followed up jointly at their respective referring centers and NMU thyroid clinic. The referring physician or NMU physician decided on the outcome of the radioactive iodine therapy after clinical and biochemical assessments. Each patient after ^{131}I treatment was followed up at 3 month intervals for 6 months.

Biochemical investigations

At the diagnosis of hyperthyroidism and during follow-up, FT4 and TSH levels were assessed at the referring hospitals or at NMU. The Radio Immuno-Assay (RIA) method is widely used to measure the FT4 and TSH levels. The normal reference range used for serum FT4 was 9.9 –24.3 pmol/L (0.8 – 1.9 ng/dl), and 0.25 – 4.2 mU/L for serum TSH.

The outcome of radioactive iodine therapy

Patients who received ^{131}I were categorized according to the thyroid status at 6 months, *i.e*., euthyroidism, hypothyroidism, or hyperthyroidism, based on the clinical and biochemical findings. Therapeutic success was considered at 6 months after ^{131}I therapy if a patient was euthyroid or permanently hypothyroid.

Persistent hyperthyroidism at 6 months was considered as therapeutic failure. Permanent hypothyroidism was considered after 3 months from ^{131}I therapy, if FT4 was low and TSH elevated, with or without hypothyroid symptoms requiring indefinite thyroxine replacement. This can avoid confusion with transient hypothyroidism which may occur during the first 3 months after ^{131}I therapy.

Discontinuation of antithyroid drugs

It is a routine practice to discontinue ATD at least 7 days before ^{131}I administration. Depending on the number of days patients were off carbimazole, they were classified into two groups; 3–7 days and 8–30 days of carbimazole discontinuation prior to ^{131}I administration.

Ethical clearance

Ethical clearance for this study was granted by the Ethical Clearance Committee, Faculty of Medicine, University of Peradeniya. Informed written consent was obtained before recruiting the patients for the study. An interviewer-administered questionnaire was used for the data collection. A code number was used to identify the patients and no personal identification detail was used in the questionnaire.

Data analysis

Data was entered in SPSS and statistical analysis was done using the SPSS version 25. The results were considered statistically significant at p value ≤ 0.05. The Chi-Square test was used to compare the difference in the outcome between carbimazole discontinuation for 3–7 days vs 8–30 days.

RESULTS AND DISCUSSION

Of the total of 89 patients, the majority were females, including 53 females (59.6 %) and 36 males (40.4 %). The underlying cause for hyperthyroidism in most was Graves' disease (N = 67, 75.3 %); in the rest it was TMNG (N = 22, 24.7 %). The mean age of the male and female patients in the whole study group was 55.00 years (SD = 12.89) and 49.19 years (SD = 13.98), respectively. The mean age of GD patients was 50.28 years (SD = 14.76) and TMNG patients was 55.36 years (SD = 9.55).

By the end of 6 months after ^{131}I administration, the total study population had 22.5 % (N = 20) of euthyroid patients, 52.8 % (N = 47) of hypothyroid and 24.7 % (N = 22) of hyperthyroid patients. Among the GD patients, 17.9 % remained euthyroid, 59.7 % were hypothyroid and 22.4 % were hyperthyroid. Among TMNG patients, 31.8 % were hypothyroid, 36.4 % remained euthyroid and 31.8 % were hyperthyroid at 6 months.

Depending on the thyroid status at 6 months after ^{131}I treatment, the therapeutic outcomes of ^{131}I were considered as therapeutic success (either euthyroid or hypothyroid) and therapeutic failure (persistent hyperthyroidism) (DeGroot *et al.*, 1990; Leslie *et al.*, 2003; Jaiswal *et al.*, 2014). In this study, 75.3 % (N = 67) of the total study population had shown therapeutic success while 24.7 % (N = 22) had a therapeutic failure. When considering different aetiologies of hyperthyroidism, 77.6 % of GD patients showed therapeutic success and 22.4 % had a therapeutic failure, while 68.2 % of the TMNG patients showed therapeutic success and 31.8 % showed therapeutic failure.

Pretreatment carbimazole discontinuation before ^{131}I therapy

The analysis revealed that carbimazole was withheld from all patients in this study group before ^{131}I treatment. Carbimazole had been withheld for a minimum of 3 days and a maximum of 30 days, with a mean of 14.15 days (SD = 7.18) in the total study population. The GD patients had 5 days as the minimum, and a maximum of 30 days, with a mean of 13.70 days (SD = 6.91). TMNG patients had 3 days as the minimum drug free days, and a maximum of 30 days, with a mean of 15.50 days (SD = 7.96).

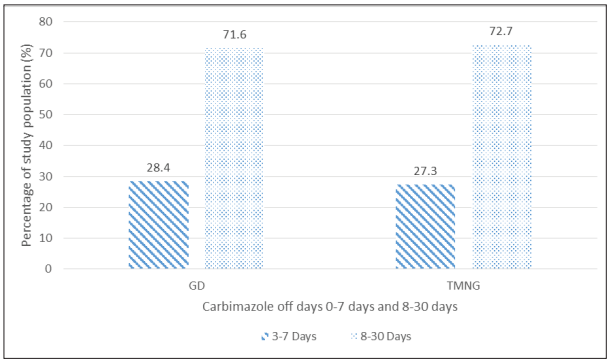

Figure 1: Carbimazole off for 3–7days and 8–30 days in GD and TMNG patients

The number of drug free days was classified as 3–7 days and 8–30 days for purposes of analysis. Results showed that 71.9 % of the total population had been off carbimazole for 8–30 days (mean no. of days = 17.03,

SD = 6.45) and 28.1 % for 3 –7 days (mean no. of days = 6.76, SD = 0.88). When the different aetiologies were considered, 71.6 % of GD patients (mean no. of days = 16.40, SD = 6.39) and 72.7 % of TMNG patients (mean no. of days = 18.94, SD = 6.45) were carbimazole free for 8–30 days. However, the remaining one third received ^{131}I while they were off carbimazole for less than a week (3–7 days); for GD patients, mean no. of days = 6.89, SD = 0.46, and for TMNG patients, mean no. of days = 6.33, SD = 1.63 (Figure 1).

Carbimazole discontinued for 3–7 days and 8–30 days vs thyroid status at 6 months after ^{131}I therapy

The difference in thyroid status at 6 months was compared between the groups, *i.e.*, carbimazole discontinued for 3–7 days and 8–30 days, and the results showed no statistically significant difference in thyroid status between them for the whole study population (Chi-square value = 0.866, p value = 0.648). This analysis also showed that there was no significant difference in thyroid status within the GD patients (Chi-square value = 0.264, p value = 0.876) and the TMNG patients (Chi-square value = 1.743, p value = 0.418) (Table 1).

Table 1: Comparison of thyroid status at 6 months among 8–30 and 3–7 ATD free days

	Total sample		GD		TMNG	
	8-30	3-7	8-30	3-7	8-30	3-7
Euthyroid %	17.9	4.5	13.4	4.5	31.8	4.6
Hypothyroid %	37.1	15.7	43.3	16.4	18.2	13.6
Hyperthyroid %	16.9	7.9	14.9	7.5	22.7	9.1
P value	0.648		0.876		0.418	

Therapeutic success, failure of ^{131}I therapy vs Carbimazole free for 3-7 days and 8–30 days

The total study population had 55.1 % therapeutic success and 16.9 % therapeutic failure among patients carbimazole free for 8–30 days, and a further 20.2 % of therapeutic success and 7.8 % of therapeutic failure among patients who were carbimazole free for 3–7 days. Even though good therapeutic success was noticed among those who had discontinued carbimazole for 8–30 days, there was no statistical difference between the patients who had done so for 8–30 days and for 3–7 days in the ^{131}I therapy outcome, within the total study sample (Chi-square = 0.201, p value=0.654), GD and TMNG patients (Table 2).

Table 2: ^{131}I therapy outcome vs carbimazole off 8–30 days or 3–7 days

	GD		TMNG	
	8-30	3-7	8-30	3-7
Therapeutic success	56.7 %	20.9 %	50%	18.2 %
Therapeutic failure	14.9 %	7.5 %	22.7 %	9.1 %
Chi square value	0.235		0.009	
P value	0.628		0.926	

ATD can decrease the radiosensitivity of thyrocytes by altering the biokinetics of ^{131}I and the free radical scavenger properties, reducing the absorption of ^{131}I, inhibiting thyroid peroxidase enzyme, and reducing the effective half-life of ^{131}I (Walter *et al.*, 2005). These effects are mostly seen among patients treated with propylthiouracil compared to methimazole or carbimazole. To overcome these inhibitory effects as a general rule, all the patients are advised to stop the antithyroid drugs at least 7 days before ^{131}I therapy (Wilson *et al.*, 1990; Sabri *et al*., 1999; Urbannek *et al*., 2001; Walter *et al.*, 2007; Oszukowska *et al.*, 2010).

This study found a therapeutic success in 75.3% of hyperthyroid patients after 10 mCi (370 MBq) ^{131}I therapy. This is compatible with several other previous studies where the patients were pretreated with carbimazole and given 10 mCi ^{131}I activity (Bogazzi *et al.,* 1999; Andrade *et al.*, 2001; Leslie *et al.*, 2003; Walter *et al.*, 2005; El Refaei and Shawkat, 2008; Prasanna Kumar & Shivaprasad, 2015).

Effect of the number of pretreatment carbimazole free days on the ^{131}I therapy outcome

Antithyroid drugs are given before the ^{131}I therapy to prevent exacerbation of thyroid crisis and to prevent the aggravation of cardiac related morbidity and mortality (Bonnema *et al.*, 2011). There are various suggestions about the number of days in which antithyroid drugs should be withdrawn before ^{131}I therapy, to achieve satisfactory radioactive iodine uptake by the thyroid (Oszukowska *et al.*, 2010). The common recommendations are to stop the antithyroid drugs for 7 days before ^{131}I administration, while some centres recommend stopping at least 2–3 days before ^{131}I administration (Lewis *et al.*, 2013; Prasanna Kumar & Shivaprasad, 2015). Discontinuing the antithyroid drugs for 7 days or less has shown a benefit with a large activity of ^{131}I. However, for a low dose of ^{131}I treatment, the discontinuation of ATD required more than 7 days (Walter *et al*., 2009).

Carbimazole had been withdrawn from all the study subjects in this study group before ^{131}I treatment. Both GD and TMNG patients did not show a significant difference in the therapeutic outcome after 6 months from ^{131}I therapy, between patients who were off carbimazole for less than seven days or more than seven days. The minimum number of carbimazole free days were 3 for the TMNG patients and 5 for the GD patients. A similar therapeutic success rate has been noted with a previous study where carbimazole has been used as the pretreatment antithyroid drug and discontinued prior to the ^{131}I therapy (Bogazzi *et al.*, 1999).

The main reason to withdraw antithyroid drugs before ^{131}I therapy is to increase the effectiveness of ^{131}I therapy. Studies have shown that withdrawing carbimazole 2–7 days before ^{131}I therapy leads to prolongation of biological half-time of ^{131}I, increases the uptake of radioactive iodine in thyrocytes, activates the thyroid peroxidase enzyme, and increases iodine organification. These mechanisms increase the therapeutic effect of ^{131}I by more than 50 % (Urbannek *et al.*, 2001; Dunkelmann *et al.*, 2007). Many studies have recommended to withdraw antithyroid drugs 3–7 days before the ^{131}I therapy (Andrade *et al.*, 2001; Bonnema *et al.*, 2002; Eschmann *et al.*, 2006; Kubota *et al*., 2006; Walter *et al.*, 2006). However, administering ^{131}I while continuing antithyroid drugs gives worse therapeutic outcomes to a greater extent (Bonnema *et al*., 2006).

Patients with GD have a shorter biological half-time for ^{131}I compared to the TMNG patients. This biological half-time is further reduced in hyperthyroid patients if they are given concurrent antithyroid drugs with ^{131}I. However, both GD and TMNG are affected similarly by the antithyroid agents (Körber *et al.*, 2001). The findings in this study also showed similar results with the number of carbimazole free days in both GD and TMNG compared to the ^{131}I therapy outcome, because both aetiologies did not have significant differences in the therapeutic outcome as a result of the number of carbimazole free days.

There are a few recommendations to withdraw antithyroid drugs for more than 7 days prior to ^{131}I therapy. These studies have observed that the therapeutic effects improve with lengthening the intervals between the antithyroid drugs and the ^{131}I treatment (Einhorn & Säterborg, 1962). But this benefit has been linked to smaller activities of ^{131}I treatment (Dunkelmann *et al*., 2007). The findings of the present study are in contrast to this recommendation. There was no difference in the ^{131}I therapy outcome with 10 mCi activity among patients who were off carbimazole for 3–7 days or 8–30 days.

The discontinuation of antithyroid drugs prior to the ^{131}I therapy can be individualized depending on the severity of the disease, type of antithyroid drug, and the associated comorbidities of the patients. Studies have provided evidence that carbimazole has a smaller effect on ^{131}I therapy outcome compared to propylthiouracil, and that the latter requires a longer duration of discontinuation. Patients with arrhythmia, myocardial insufficiency, and arterial hypertension may experience exacerbation as a result of worsening thyrotoxicosis due to prolonged withdrawal of the antithyroid drug. Taking these factors into consideration, the duration of discontinuing ATD should be decided on a case by case basis before the ^{131}I therapy (Dunkelmann *et al.*, 2007). This study showed that withdrawing carbimazole 3-7 days prior to ^{131}I administration had an adequate level of outcome for radioactive iodine treatment, which was similar to previous studies, while showing no extra benefits for discontinuing ATD for more than 7 days. This may be due to fixed larger activities of ^{131}I (10 mCi) used among this study population (Dunkelmann *et al.*, 2007). But the intracellular findings have shown that, one day after withdrawal of carbimazole, the intrathyroidal kinetics of ^{131}I are still altered but they are normalized 2 days after discontinuation. As a consequence, carbimazole or methimazole medication should be discontinued at least 2 days before ^{131}I therapy (Dunkelmann *et al.*, 2007). This principle is further strengthened by our findings.

CONCLUSIONS

There was no difference in 10 mCi radioactive iodine therapy outcome at 6 months between patients who were off carbimazole for 3–7 days and 8–30 days. There is no extra benefit in the outcome of withdrawing carbimazole more than 7 days. However, this pretreatment discontinuation can be decided on individual basis depending on the comorbidities associated.

Conflict of interests

None.

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