Long-term carbimazole pretreatment reduces the efficacy of radioiodine therapy

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ABSTRACT

Introduction: Data from several studies suggest that pretreatment with antithyroid drugs (ATD) before \( ^{131}I \) increases the risk of treatment failure. This effect has been demonstrated more consistently with propylthiouracil than with carbimazole (CMZ) or methimazole (MMI). Men with Graves’ disease (GD) have a lower rate of remission with \( ^{131}I \) compared to women and the impact of long-term ATD pretreatment on the success of \( ^{131}I \) is unknown. The objective of our study was to compare the efficacy of fixed doses of radioiodine between patients with and without long-term CMZ pretreatment. Materials and Methods: We performed a retrospective study on 335 male patients with GD treated with \( ^{131}I \) from 1998 to 2008. 148 patients had been pretreated with CMZ, and the remaining 187 patients received \( ^{131}I \) without pretreatment. We compared the success rate of a single dose of \( ^{131}I \), between patients with and without long-term CMZ pretreatment. Results: The success rate of a single dose of \( ^{131}I \) was significantly higher in patients without pretreatment than in patients who were pretreated with CMZ (91.4% vs. 82.3%, \( P = 0.01 \)). The rate of hypothyroidism in the first 6 months after \( ^{131}I \) therapy was significantly higher in patients without pretreatment (55.1% vs. 44.6%, \( P = 0.05 \)). There was also a trend for higher cumulative rate of hypothyroidism at last follow-up in nonpretreated patients (78.1% vs. 69.7%). Conclusion: Male patients with Graves’ hyperthyroidism pretreated with CMZ have lower efficacy with \( ^{131}I \) therapy compared to nonpretreated patients. CMZ pretreatment given for a prolonged period reduces the efficacy of \( ^{131}I \) therapy.

Key words: Antithyroid drugs, carbimazole, Graves’ hyperthyroidism, pretreatment, radioiodine

INTRODUCTION

Radioactive iodine (RAI) therapy has been used as a first line of treatment for Graves’ hyperthyroidism (Graves’ disease [GD]) for more than seven decades and is still the treatment of choice in many parts of the world. It’s a common practice to pretreat patients with antithyroid drugs (ATD) prior to radioiodine ablation, to restore euthyroidism and to prevent exacerbation of the thyrotoxic state seen in some patients after radioiodine therapy. ATD have a radioprotective effect and pretreatment with ATD has been shown to increase the risk of treatment failure with subsequent \( ^{131}I \). This effect has been demonstrated more consistently with propylthiouracil (PTU) than with carbimazole (CMZ) or methimazole (MMI). It has been recommended that ATD should be stopped 3–5 days before \( ^{131}I \) to reduce the interference of ATD with the efficacy of radioiodine therapy. Men with GD have a lower rate of remission compared to women and the impact of long-term pretreatment with ATD on the efficacy of radioiodine treatment in men has not been adequately evaluated. The objective of this retrospective study, in men with GD, was to compare the efficacy of fixed doses of radioiodine between patients with and without long-term CMZ pretreatment.

MATERIALS AND METHODS

We reviewed the case records of 464 male patients with GD treated at M. S. Ramaiah Medical College, Bangalore, with \( ^{131}I \), in the period between 1998 and
2008. GD was defined as the occurrence of biochemical hyperthyroidism (raised serum total/free T4 concentration and undetectable/low thyroid stimulating hormone [TSH]) together with the presence of at least two of the following: a palpable diffuse goiter, diffusely increased uptake on the technetium 99 m thyroid scan, elevated titers of thyroid peroxidase and/or TSH receptor autoantibodies, and/or the presence of ophthalmopathy. The inclusion criteria were: radionuclide studies and thyroid function tests consistent with GD, a recipient of $^{131}$I therapy, at least 1-year of follow-up data available post $^{131}$I therapy and discontinuation of CMZ therapy at least 5–7 days before radioiodine administration. Exclusion criteria included therapy with any ATD other than CMZ or ATD therapy during radioiodine therapy. Patients pretreated for <3 months were also excluded. Patients were divided into two groups—patients pretreated with CMZ as a primary long-term therapy that subsequently received $^{131}$I and untreated newly diagnosed patients who were given $^{131}$I alone without ATD pretreatment. In patients opting for ATD as primary therapeutic option, our policy was to administer them for 12–24 months and patients who were biochemically hyperthyroid or who required a dosage of >10 mg/d of CMZ to maintain euthyroidism at the end of therapy would then be advised to take $^{131}$I therapy.

Three hundred and thirty-five patients met the study criteria. Of the 335 patients, 148 patients had been pretreated with ATD and remaining 187 patients received $^{131}$I without pretreatment. Mean duration of ATD therapy before $^{131}$I was 23.1 months. Patients were treated with a single fixed dose of $^{131}$I based on the uptake of radioiodine and thyroid size. The dose of $^{131}$I varied from 5 to 15 millicurie (mCi). In patients pretreated with ATD, the drugs were withdrawn 5–7 days before radioiodine therapy. Following RAI treatment, thyroid status was monitored every 2–3 months during the 1st year and 3–6 monthly thereafter. All the patients within the study group were followed up for at least 12 months after treatment. Cure of hyperthyroidism after $^{131}$I was defined as euthyroid status for 6 months off treatment or the need for levothyroxine replacement for biochemical hypothyroidism.

Statistical methods
Data are reported as mean and standard deviation for the continuous variables, number and percentage for the categorical variables. Student’s $t$-test (unpaired $t$-test) was used to compare the outcome results between drug-naive patients and patients who were previously on ATD. Chi-squared test was used to compare the observed frequencies of palpable goiter and ophthalmopathy between the two study groups. Two sample proportion test was used to compare the success rate of a single dose of $^{131}$I and differences in the rates of worsening of ophthalmopathy (%) between the study groups. Statistical analyses were done using StataCorp 12. $P < 0.05$ was set as statistically significant.

RESULTS
The baseline demographic, clinical, and laboratory characteristics of the cohort are summarized in Table 1. The prevalence of ophthalmopathy was not significantly different between the two groups. The overall success rate of a single dose of $^{131}$I for the entire cohort was 80.2% (275/335) and the cumulative rate of hypothyroidism at 1-year was 64.5%.

A mean dose of $^{131}$I administered was similar in the two groups. The success rate of a single dose of $^{131}$I was significantly higher in patients without pretreatment than in patients who were pretreated with CMZ (91.4% vs. 82.3%, $P = 0.01$) [Figure 1]. The rate of hypothyroidism within the first 6 months after $^{131}$I therapy was significantly higher in patients without pretreatment (55.1% vs. 44.6%, $P = 0.05$). The rate of hypothyroidism between 6 months and 1-year after $^{131}$I therapy was not significantly different between the two groups (12.2% vs. 16.9%, $P = 0.2$). There was a trend for a higher cumulative rate of hypothyroidism at last follow-up in the drug-naive patients (78.1% vs. 69.7%), though it did not quite achieve the threshold for statistical significance ($P = 0.08$) [Table 2]. There was also a nonsignificant trend for a shorter mean duration for the development of hypothyroidism in the drug-naive patients. The rate of worsening of ophthalmopathy was not significantly different between the two groups. Cumulative rates of hypothyroidism between 1 and 6 months and 6 and 12 months were 55.1% and 12.2% respectively. 13.3% of drug-naive patients and 12.8% of patients who had previously received ATD before $^{131}$I were euthyroid at the last follow-up without the need for levothyroxine replacement.

| Table 1: Baseline characteristics of the two study groups |
|-----------------------------------------------------|
| Patients without ATD pretreatment (n=187) (%) | Patients pretreated with ATD (n=148) (%) | $P$ |
| Age (mean±SD) | 39.25±11.03 | 40.76±10.25 | 0.20 |
| Palpable goiter | | | |
| None | 13 (9) | 18 (12.2) | 0.05 |
| Small | 92 (49.3) | 87 (58.7) | |
| Medium/large | 72 (38.7) | 43 (29.1) | |
| Ophthalmopathy | | | |
| None | 144 (77.0) | 107 (72.3) | 0.37 |
| Present | 43 (23.0) | 41 (27.7) | |
| Total T4 (mean±SD) | 20.41±4.3 | 19.63±4.1 | 0.09 |

$P<0.05$ significant. SD: Standard deviation, ATD: Antithyroid drugs
DISCUSSION

Our data demonstrate that male patients with Graves’ hyperthyroidism pretreated with CMZ have reduced efficacy with subsequent $^{131}$I therapy. Cumulative hypothyroidism and hypothyroidism within 6 months after $^{131}$I were also lower in them compared to patients who were not pretreated.

Although radioiodine is considered a safe and effective treatment for GD, controversies remain on the optimal method for calculating the dose and the most appropriate dose regimen. Achieving long-term euthyroidism appears to be a futile objective and most series report high rates of cumulative hypothyroidism after $^{131}$I.[10–12] Our findings are in concurrence with these studies, with two-thirds of patients developing hypothyroidism within 1 year. In our study, the success rate of $^{131}$I without ATD pretreatment was 91%. Cure rates of 67%–95% have been reported after different doses of $^{131}$I (5–12.3 mCi) and studies employing higher doses (>10 mCi) have reported success rates between 86% and 95%.[10–17] A study from south India reported a success rate of 95% with a fixed dose of 10 mCi in GD.[18]

A cure rate of 82% seen in patients pretreated with CMZ. The results are comparable to a previous study of 58 patients that reported a success rate of 82% of a fixed dose of RAI in patients on long-term CMZ.[19] Another study of 61 patients found a success rate of 80% in patients pretreated with MMI.[7] A retrospective study in patients of GD on long-term PTU reported a success rate of 83% for $^{131}$I when PTU was stopped at least a week before $^{131}$I therapy and 71% when PTU was stopped for 4–7 days. $^{131}$I administered without PTU pretreatment had a success rate of 91%.[20] A prospective study reported a success rate of 83% at 1 year in patients pretreated with CMZ when it was stopped 3 days before $^{131}$I.[21]

Simultaneous use of ATD with RAI has consistently been shown to result in lower efficacy and higher failure rate than treatment with RAI alone.[21–25] However, studies have demonstrated that pretreatment with ATD leads to a higher failure rate even if the drugs are discontinued 4–7 days before RAI therapy and not restarted posttherapy. This effect has been demonstrated consistently with PTU and studies on CMZ/MMI yielded conflicting results. Hancock et al., found that PTU discontinued 4–7 days before radioiodine dosing was associated with a significant increase in the failure rate of subsequent radioiodine therapy.[20] Two other studies also reported that PTU pretreatment significantly reduced the efficacy of $^{131}$I therapy.[8,26] Imseis et al., found that PTU (but not MMI) may reduce the therapeutic efficacy of subsequent $^{131}$I when they were discontinued 5–55 days before radioiodine treatment.[15]

Goolden and Fraser found equal cure rates from $^{131}$I with and without CMZ pretreatment, when CMZ was discontinued 3–5 days before $^{131}$I therapy.[27] Two randomized controlled trials (RCTs) reported that MMI pretreatment didn’t interfere with the efficacy of $^{131}$I therapy.[7,28] Another study found no interference of CMZ treatment with the efficacy of $^{131}$I when it was discontinued 5–7 days before radioiodine therapy, but the success rate was much lower if it was simultaneously administered with $^{131}$I therapy.[22] In another study, pretreatment with MMI reduced the efficacy of $^{131}$I only when it was administered on the day of $^{131}$I therapy.[23]

However, a few other studies have reported that CMZ or MMI pretreatment reduces the efficacy of $^{131}$I. Connell et al., reported that CMZ stopped 5 days before $^{131}$I reduced the rate of hypothyroidism at 1 year compared to nonpretreated patients.[29] Two other studies reported that CMZ pretreatment reduced the efficacy of $^{131}$I therapy.[4,30] ATD, including CMZ, given within 1 week after radioiodine treatment was found to reduce the efficacy of $^{131}$I in a retrospective study of 206 patients.[31] A retrospective study of 360 patients with hyperthyroidism, with a follow-up range of 2–10 years, reported that ATD, including both PTU and CMZ pretreatment reduces the efficacy of radioiodine therapy. In that study, the response rate was significantly higher in the group without pretreatment (95%) as compared to patients with pretreatment (80.9%), much similar to the results of our study.[32] Another retrospective study of 449 patients with hyperthyroidism using a 550MBq fixed dose regimen found that CMZ pretreatment stopped 1 week before radioiodine therapy reduced the efficacy of radioiodine treatment.[33] Finally, a meta-analysis of 14 RCT reported that adjunctive ATD, including CMZ, were associated with an increased risk of treatment failure with $^{131}$I and reduced risk for hypothyroidism.[3]

Antithyroid drugs are used in the management of GD either as primary therapy for several months while awaiting remission of the disease or as pretreatment for several weeks prior to definitive RAI therapy. ATD are believed to have a radioprotective effect and hence interfere with and reduce the efficacy of $^{131}$I therapy. Radio resistance conferred by thioureas is believed to be due to their sulfhydryl groups.[34] As CMZ does not have a sulfhydryl group, it was proposed that it confers
The merits of our study are a large number of patients and an uniform study group. We have only examined the outcome of radioiodine therapy in a retrospective analysis. A large prospective randomized control study is warranted to further clarify the effect of pretreatment with CMZ on the efficacy of ¹³¹I therapy.

Conclusions

Male patients with Graves’ hyperthyroidism pretreated with CMZ have lower efficacy with ¹³¹I therapy compared to nonpretreated patients. CMZ pretreatment given for a prolonged period interferes with the efficacy of ¹³¹I therapy.

References

1. Cooper DS. Hyperthyroidism. Lancet 2003;362:459-68.
2. Perros P. Anti-thyroid drug treatment before radioiodine in patients with Graves’ disease: Soother or menace? Clin Endocrinol (Oxf) 2000;53:1-2.
3. Walter MA, Briel M, Christ-Crain M, Bonnema SJ, Connell J, Cooper DS, et al. Effects of antithyroid drugs on radioiodine treatment: Systematic review and meta-analysis of randomised controlled trials. BMJ 2007;334:514.
4. Koroscil TM. Thionamides alter the efficacy of radioactive iodine therapy in patients with Graves’ disease. South Med J 1995;88:831-6.
5. Imseis RE, Vanmiddlesworth LR, Massie JD, Bush AJ, Vanmiddlesworth NR. Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of iodine-131 in hyperthyroidism. J Clin Endocrinol Metab 1998;83:685-7.
6. Tuttle RM, Patience T, Budd S. Treatment with propylthiouracil before radioiodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid 1995;5:243-7.
7. Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves’ hyperthyroidism: One-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab 2001;86:3488-93.
8. Bonnema SJ, Bennedbaek FN, Veje A, Marving J, Hegedûs L. Propylthiouracil before 131I therapy of hyperthyroid diseases: Effect on cure rate evaluated by a randomized clinical trial. J Clin Endocrinol Metab 2004;89:4439-44.
9. Shi GM, Xu Q, Zhu CY, Yang YL. Influence of propylthiouracil and methimazole pre-treatment on the outcome of iodine-131 therapy in hyperthyroid patients with Graves’ disease. J Int Med Res 2009;37:576-82.
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10. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611-7.

11. Tavinhara S, Sundram FX, Chew LS. Radioiodine (I-131) therapy and the incidence of hypothyroidism. Ann Acad Med Singapore 1997;26:128-31.

12. Alexander EK, Larsen PR. High dose of (131)I therapy for the treatment of hyperthyroidism caused by Graves’ disease. J Clin Endocrinol Metab 2002;87:1073-7.

13. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves’ hyperthyroidism. J Clin Endocrinol Metab 2003;88:978-83.

14. Howarth D, Epstein M, Lan L, Tan P, Booker J. Determination of the optimal minimum radioiodine dose in patients with Graves’ disease: A clinical outcome study. Eur J Nucl Med 2001;28:1489-95.

15. Metso S, Jaatinen P, Huhtala L, Luukkaala T, Oksala H, Salmi J. Long-term follow-up study of radioiodine treatment of hyperthyroidism. Clin Endocrinol (Oxf) 2004;61:641-8.

16. Bringmann IM, van Leeuwen BL, Hennemann G, Beckett GJ, Toft AD. Outcome of treatment of hyperthyroidism. J Endocrinol Invest 1999;22:250-6.

17. Tarantini B, Ciuti C, Di Cairano G, Guarino E, Mazzuccato P, Montanaro A, et al. Effectiveness of radioiodine (131-I) as definitive therapy in patients with autoimmune and non-autoimmune hyperthyroidism. J Endocrinol Invest 2006;29:594-8.

18. Shinto AS, Pachen L, Sreekanth TK. Fixed dose radioactive iodine therapy in hyperthyroidism: Outcome and factors affecting it in a region in South India. Thyroid Sci 2010;5:1-7.

19. El Rafaey SM, Shawkat W. Long-term carbimazole intake does not affect success rate of radioactive I131* in treatment of Graves’ hyperthyroidism. Nucl Med Commun 2008;29:642-8.

20. Hancock LD, Tuttle RM, LeMar H, Bauman J, Patiente T. The effect of prophylactioid on subsequent radioactive iodine therapy in Graves’ disease. Clin Endocrinol (Oxf) 1997;47:425-30.

21. Walter MA, Christ-Crain M, Schindler C, Müller-Brand J, Müller B. Outcome of radioiodine therapy without, on or 3 days off carbimazole: A prospective interventional three-group comparison. Eur J Nucl Med Mol Imaging 2006;33:730-7.

22. Sabri O, Zipnny M, Schulz G, Schreckenberger M, Reinartz P, Willmes K, et al. Success rate of radioiodine therapy in Graves’ disease: The influence of thyrostat medication. J Clin Endocrinol Metab 1999;84:1229-33.

23. Walter MA, Schindler C, Christ-Crain M, Müller-Brand J, Müller B. Different strategies to overcome the effect of carbimazole on high- and low-dose radioiodine therapy: Results from continuous dose-effect models. Eur J Clin Invest 2009;39:51-7.

24. Sabri O, Zipnny M, Schreckenberger M, Reinartz P, Ostwald E, Buell E. Radioiodine therapy in Graves’ disease patients with large diffuse goiters treated with or without carbimazole at the time of radioiodine therapy. Thyroid 1999;9:1181-8.

25. Pirat E, Zaletel K, Gabersček S, Hjøjer S. The outcome of 131I treatment in Graves’ patients pretreated or not with methimazole. Helv J Nucl Med 2011;14:25-9.

26. Santos RB, Romaldini JH, Ward LS. Propylthiouracil reduces the effectiveness of radioiodine treatment in hyperthyroid patients with Graves’ disease. Thyroid 2004;14:525-30.

27. Gooden AW, Fraser TR. Effect of pretreatment with carbimazole in patients with thyrotoxicosis subsequently treated with radioactive iodine. Br Med J 1969;3:443-4.

28. Braga M, Walpert N, Burch HB, Solomon BL, Cooper DS. The effect of methimazole on cure rates after radioiodine treatment for Graves’ hyperthyroidism: A randomized clinical trial. Thyroid 2002;12:135-9.

29. Connell JM, Hilditch TE, Mc Crudden DC, Robertson J, Alexander WD. Effect of pretreatment with carbimazole on early outcome following radio-iodine (131I) therapy. Eur J Nucl Med 1984;9:464-6.

30. Franklyn JA, Daykin J, Holder R, Sheppard MC. Radioiodine therapy compared in patients with toxic nodular or Graves’ hyperthyroidism. J Clin Endocrinol Metab 1995;88:175-80.

31. Velkeniers B, Cytryn R, Vanhaelen L, Jonckheer MH. Treatment of hyperthyroidism with radioactive iodine: Adjunctive therapy with antithyroid drugs reconsidered. Lancet 1988;1:1127-9.

32. Ghabban WK, Zirie MA, Al-Khateeb DA, Jayyousi AA, Mobaydeth HM, El-Aloosy AS. Radioiodine treatment of hyperthyroidism. Success rate and influence of thyrostatic medication. Saudi Med J 2003;24:347-51.

33. Lewis A, Atkinson B, Bell P, Courtney H, McCance D, Mullan K, et al. Outcome of 131I therapy in hyperthyroidism using a 550MBq fixed dose regimen. Ulster Med J 2013;82:85-8.

34. Einhorn J, Saterborg NE. Antithyroid drugs in iodine 131 therapy of hyperthyroidism. Acta radiol 1962;58:161-7.

35. Yau JS, Chu KS, Li JK, Chan KW, Lau IT, Yum SW, et al. Usage of a fixed dose of radioactive iodine for the treatment of hyperthyroidism: One-year outcome in a regional hospital in Hong Kong. Hong Kong Med J 2009;15:267-73.

36. Collier A, Ghosh S, Hair M, Malik J, McGarvie J. Comparison of two fixed activities of radioiodine therapy (370 vs 555 MBq) in patients with Graves’ disease. Hormones (Athens) 2009;8:273-8.

37. Bonnema SJ, Bartalena L, Toft AD, Hegedüs L. Controversies in radioiodine therapy: Relation to ophthalmopathy, the possible radioprotective effect of antithyroid drugs, and use in large goiters. Eur J Endocrinol 2002;147:1-11.

38. Hegedüs L. Treatment of Graves’ hyperthyroidism: Evidence-based and emerging modalities. Endocrinol Metab Clin North Am 2009;38:355-71, ix.

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