

Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective To determine the effect of adjunctive antithyroid drugs on the risk of treatment failure, hypothyroidism, and adverse events after radioiodine treatment.

Design Meta-analysis.

Data sources Electronic databases (Cochrane central register of controlled trials, Medline, Embase) searched to August 2006 and contact with experts.

Review methods Three reviewers independently assessed trial eligibility and quality. Pooled relative risks for treatment failure and hypothyroidism after radioiodine treatment with and without adjunctive antithyroid drugs were calculated with a random effects model.

Results We identified 14 relevant randomised controlled trials with a total of 1306 participants. Adjunctive antithyroid medication was associated with an increased risk of treatment failure (relative risk 1.28, 95% confidence interval 1.07 to 1.52; $P=0.006$) and a reduced risk for hypothyroidism (0.68, 0.53 to 0.87; $P=0.006$) after radioiodine treatment. We found no difference in summary estimates for the different antithyroid drugs or for whether antithyroid drugs were given before or after radioiodine treatment.

Conclusions Antithyroid drugs potentially increase rates of failure and reduce rates of hypothyroidism if they are given in the week before or after radioiodine treatment, respectively.

INTRODUCTION

Radioiodine treatment was introduced in 1941 and has become a cornerstone in the treatment of hyperthyroidism. Short term side effects include an acute rise in thyroid hormone concentrations with potential clinical exacerbation and increased cardiovascular risk. Long term side effects include hypothyroidism, which requires permanent thyroid hormone substitution.

The antithyroid drugs propylthiouracil and methimazole and its precursor carbimazole are commonly used to alleviate symptoms of hyperthyroidism and to diminish the short and long term side effects of radioiodine treatment.^{1,2} There is disagreement, however, about the beneficial and detrimental effects and the optimal sequencing of the different antithyroid drugs before or after radioiodine treatment. Current recom-

mendations are based on single trials and narrative reviews.

We conducted a systematic review and meta-analysis of randomised controlled trials to compare the rates of treatment failure and the short and long term side effects in people with hyperthyroidism receiving radioiodine treatment with or without adjunctive antithyroid drugs.

METHODS

Search strategy—We searched the electronic libraries Medline, Embase, and the Cochrane central register of controlled trials for randomised and non-randomised studies comparing adjunctive antithyroid drugs on the outcome of radioiodine treatment. We also searched relevant websites and reference lists and contacted experts and authors where needed. See bmj.com for details.

Study selection—Studies had to be randomised controlled trials in adults with hyperthyroidism that examined the outcome of radioiodine treatment with adjunctive antithyroid drugs and with a minimum follow-up of six months. We excluded studies that intended to deliver different target doses of radioiodine to compensate for a potential effect of the antithyroid drug. See bmj.com for studies that were not randomised but otherwise fulfilled inclusion criteria. Three investigators independently assessed study eligibility and quality and resolved any disagreement by consensus. We assessed the quality of trials according to concealment of treatment allocation, completeness of follow-up, blinding and performance of a sample size calculation. Main outcome measures were rates of treatment failure, hypothyroidism, and adverse effects 6-12 months after radioiodine treatment. Radioiodine treatment was considered as successful if hyperthyroidism was eliminated according to the definition used in the corresponding trials.

Quantitative data synthesis—We pooled treatment effects and calculated risks ratios for the main outcomes in the treatment and control groups using a random effects model. All comparisons were based on intention to treat. Loss of follow-up was regarded as unsuccessful treatment. We also performed a per protocol

analysis restricted to patients with complete follow-up for treatment failure and hypothyroidism. We tested for heterogeneity, measured inconsistency of treatment effects across trials, and examined the presence of a small study effect with funnel plots and Egger's test. We performed sensitivity analyses, and used logistic regression to examine the association of administered radioiodine and resulting hypothyroidism and success rates in the control arms. See bmj.com for details.

RESULTS

Fourteen randomised controlled trials met the inclusion criteria.^{w1-w14} Included trials randomly assigned

1306 patients receiving radioiodine treatment to adjunctive antithyroid drugs (n=660) or control (n=646).

Study characteristics—The included trials were published between 1952 and 2006. The quality of methods of included trials was generally poor; few studies reported adequate methods for randomisation and blinding. Different criteria were used to assess the thyroid status. Overall, 1269/1306 (97%) participants completed follow-up. The applied median dose of radioiodine varied between 158 and 585 MBq. With the exception of five trials,^{w5 w7 w8 w13 w14} reports included only patients with Graves' disease. Five trials gave antithyroid drugs before radioiodine treatment,^{w5 w6 w8 w11 w12} seven trials gave them at the same time or after,^{w1-w4 w10 w13 w14} and two trials gave them before and after.^{w7 w9}

Treatment failure—The summary risk ratio for treatment failure with adjunctive antithyroid drugs compared with control was 1.28 (95% confidence interval 1.07 to 1.52; P=0.006). There was no difference in summary estimates for different antithyroid drugs. A similar risk ratio was obtained on the basis of a per protocol analysis (1.34, 0.96 to 1.88; P=0.09). Subgroup analysis revealed a risk ratio of 1.48 (1.09 to 2.00; P=0.01) when antithyroid drugs were given before radioiodine treatment and 1.32 (1.04 to 1.68; P=0.03) when they were given simultaneously or after radioiodine treatment (fig 1). Heterogeneity among treatment effects was low. The funnel plot indicated an asymmetric distribution (Egger's test P=0.002) with a larger effect size in smaller studies. When we excluded the three smallest studies we found a significantly increased risk of treatment failure (1.21, 1.00 to 1.45; P=0.04) and lower evidence for funnel plot asymmetry (Egger's test P=0.15).

Hypothyroidism—The summary risk ratio for hypothyroidism with adjunctive antithyroid drugs compared with control was 0.68 (0.53 to 0.87; P=0.006). Again, there was no difference in summary estimates for the different antithyroid drugs. A per protocol analysis revealed a similar risk ratio (0.77, 0.54 to 1.10; P=0.15). The risk ratio was 0.76 (0.57 to 1.01; P=0.06) when antithyroid drugs were given before radioiodine treatment and 0.57 (0.41 to 0.78; P<0.001) when they were given simultaneously or after radioiodine treatment (fig 2). Heterogeneity among treatment effects was low to moderate. The funnel plot indicated an asymmetric distribution (Egger's test P=0.022) with a larger effect size in smaller studies. When we excluded the three smallest studies sensitivity analysis showed a significant reduction in risk of hypothyroidism (0.80, 0.68 to 0.95; P=0.01) and lower evidence for funnel plot asymmetry (Egger's test P=0.13).

Sensitivity analyses—We found a trend towards a higher risk of treatment failure in the two trials using fixed radioiodine doses^{w9 w12} (2.68, 0.96 to 7.44) compared with the five trials that adapted dose calculation according to uptake^{w5-w8 w11} (1.38, 1.00 to 1.91) when antithyroid drugs were given before radioiodine. We found a trend towards larger effects on

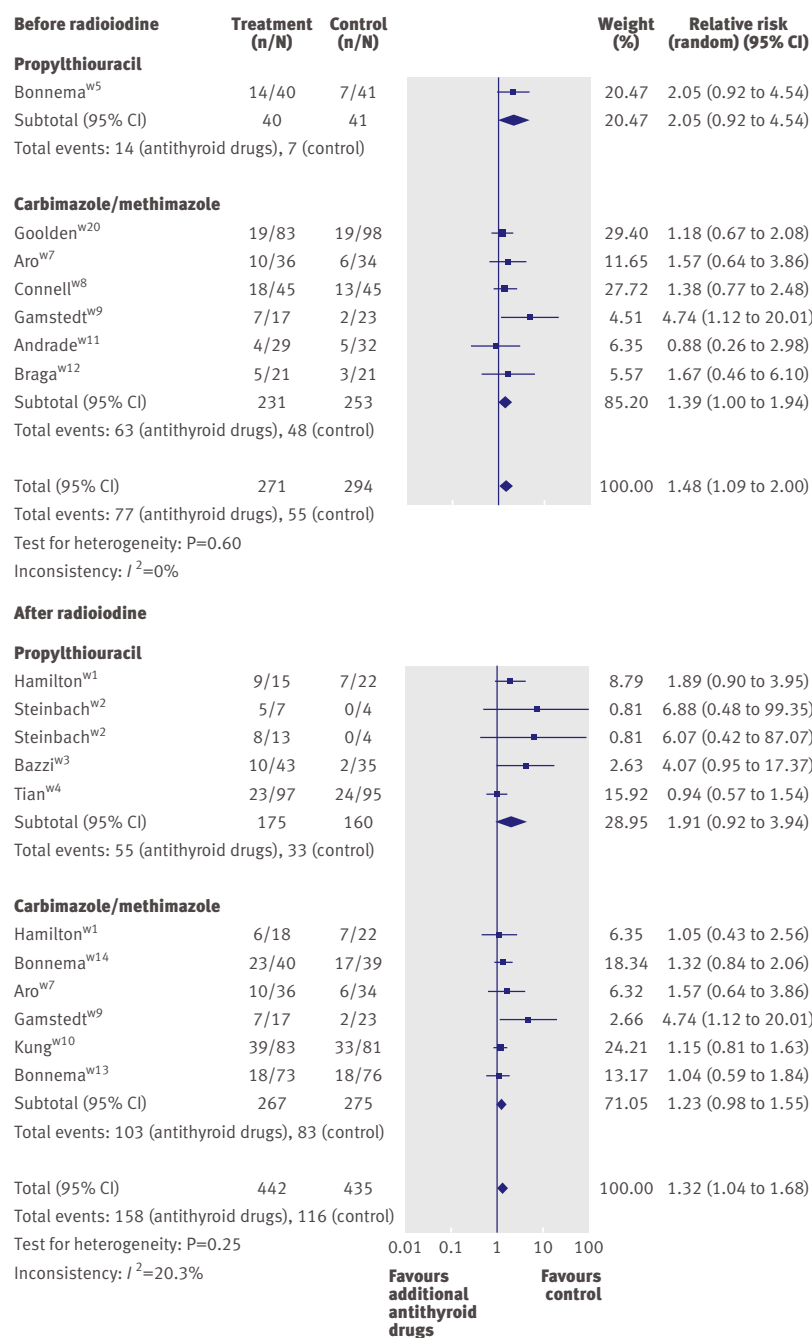


Fig 1 | Risk of treatment failure with antithyroid drugs given before or after radioiodine treatment

treatment failure (1.39, 1.00 to 1.94) and hypothyroidism (0.74, 0.54 to 1.02) in the six trials with high doses of antithyroid drug^{w1 w3 w7-w10} compared with the three trials using lower doses^{w4 w13 w14} after radioiodine (1.11, 0.83 to 1.48, for treatment failure; 0.83, 0.49 to 1.39, for hypothyroidism).

Correlation of radioiodine activity and outcome—Logistic regression showed a highly significant correlation between the administered radioiodine activity and the rates of hypothyroidism ($P<0.001$) and successful treatment ($P<0.001$).

Acute complications of antithyroid drugs and radioiodine—Adverse events with antithyroid drugs were reported

in 12/660 participants (1.8%). Pretreatment with antithyroid drugs reduced concentrations of serum thyroid hormones before radioiodine treatment and until six weeks after radioiodine treatment.^{w5 w7 w9 w11 w12}

Antithyroid drugs given with or after radioiodine treatment reduced thyroid hormone concentrations until eight weeks after radioiodine treatment.^{w7 w13 w14} New onset atrial fibrillation after radioiodine treatment was reported in 1/660 (0.2%) patients with additional antithyroid drugs and in 3/646 (0.5%) patients without additional antithyroid drugs. Death after radioiodine treatment was reported for 1/660 (0.2%) patients with and 6/646 patients (0.9%) without adjunctive antithyroid drugs.

DISCUSSION

Our meta-analysis suggests increased treatment failures if antithyroid drugs are given before, with, or after radioiodine treatment and a reduced risk of hypothyroidism, especially if antithyroid drugs are given with or after radioiodine treatment. Considering the progressive nature of the yearly increasing incidence of hypothyroidism after radioiodine treatment,^{3 w10} however, the extent of the protective effect of antithyroid drugs remains uncertain.

Our systematic review suggests that adjunctive antithyroid drugs reduce biochemical and clinical hyperthyroidism in the weeks after radioiodine treatment; however, this was not systematically monitored in all trials. We found lower cardiac morbidity and mortality with adjunctive antithyroid drugs, though this was not significant and neither event was a primary outcome. The small number of events precludes firm conclusions. Adverse events with antithyroid drugs were reported, even though the overall prevalence of 2% was lower than expected,² probably because primary trials excluded patients with known allergies.

There is an ongoing controversy about potential differences in the influence of propylthiouracil and imidazoles on radioiodine treatment.⁴⁻⁶ Our meta-analysis found no disparity, but data from non-randomised studies suggest more distinct and protracted effects with propylthiouracil than with imidazoles (see bmj.com). According to the non-randomised studies, methimazole or carbimazole could be preferable for euthyroidism.

Strengths and limitations of study

We cannot rule out publication bias, though we performed an extensive literature search. The reported methodological quality of most included trials was low, and we could not perform extensive sensitivity analyses. We also collected data from non-randomised studies that support the results of the randomised trials and indicate an effect of antithyroid drugs on radioiodine treatment even after long term withdrawal. As antithyroid drugs are widely used as first line treatment and several patients in the control arms in some studies had antithyroid drugs withdrawn several weeks before radioiodine treatment, our risk estimates for hypothyroidism and treatment failure might even be underestimated.

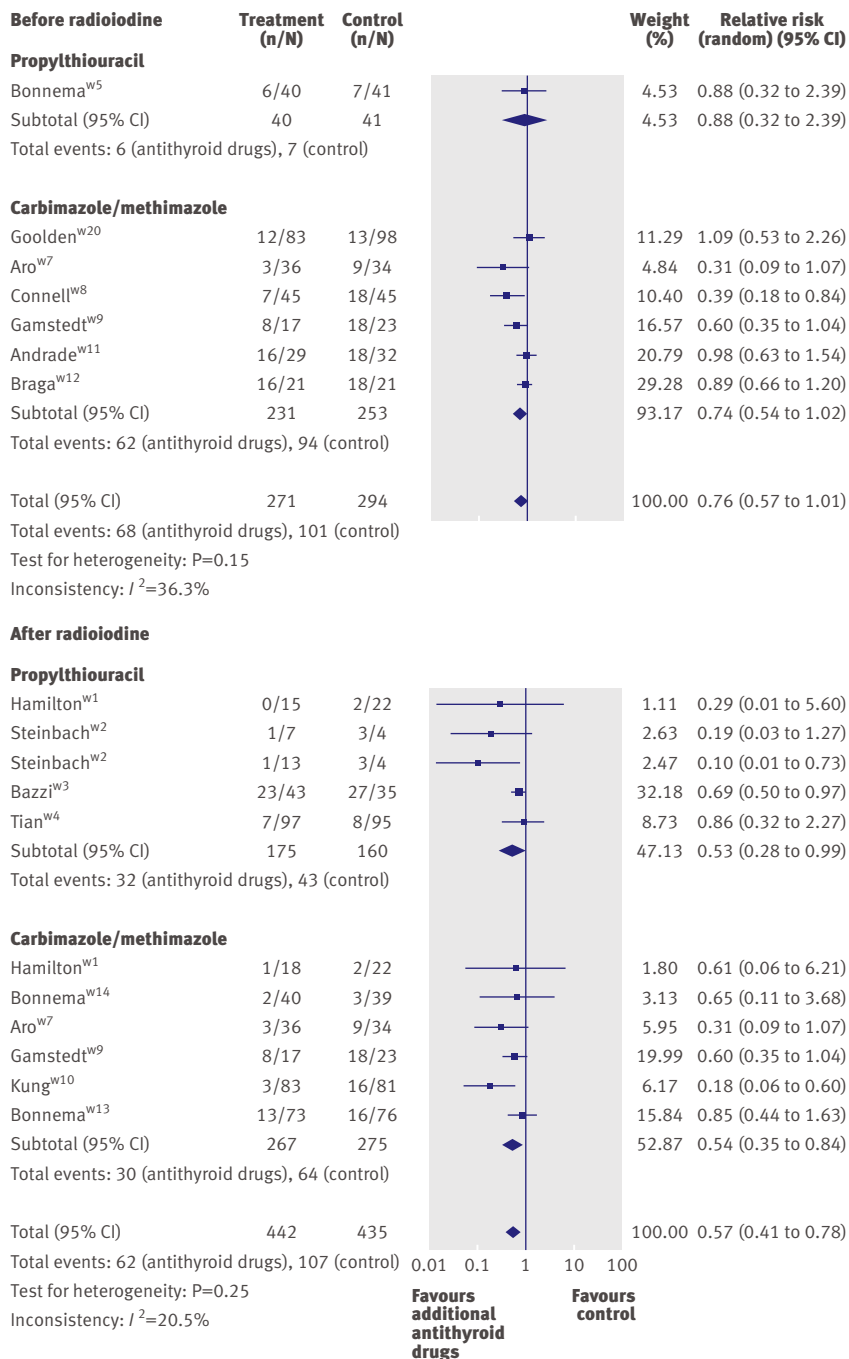


Fig 2 | Risk of hypothyroidism with antithyroid drugs given before or after radioiodine treatment

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antithyroid drugs are often used before, during, or after radioiodine treatment for hyperthyroidism

There is still disagreement about the overall beneficial and detrimental effects and the optimal sequencing of the different antithyroid drugs before or after radioiodine treatment

WHAT THIS STUDY ADDS

Adjunctive antithyroid drugs reduce the biochemical exacerbation of hyperthyroidism directly after radioiodine treatment

When given in the week before or after radioiodine, antithyroid drugs increase the failure rates and reduce the hypothyroidism rates

This meta-analysis, in contrast with the conclusions of most single trials, suggests that antithyroid drugs increase rates of failure and reduce rates of hypothyroidism when they are given in the week before or after radioiodine treatment. Results from trials included in this review, however, do not allow us to draw firm conclusions regarding the optimal interruption period of antithyroid drugs for patients undergoing radioiodine treatment to avoid both relapse of hyperthyroidism and cardiovascular complications while keeping the long term risk of hypothyroidism at an acceptable level.

Adequately powered randomised long term follow-up trials are needed to examine a potential superiority of longer discontinuation intervals.

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Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial

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ABSTRACT

Objectives To determine functional and psychological benefits of a 12 week supervised group exercise programme during treatment for early stage breast cancer, with six month follow-up.

Design Pragmatic randomised controlled prospective open trial.

Setting Three National Health Service oncology clinics in Scotland and community exercise facilities.

Participants 203 women entered the study; 177 completed the six month follow-up.

Interventions Supervised 12 week group exercise programme in addition to usual care, compared with usual care.

Main outcome measures Functional assessment of cancer therapy (FACT) questionnaire, Beck depression inventory, positive and negative affect scale, body mass index, seven day recall of physical activity, 12 minute walk test, and assessment of shoulder mobility.

Results Mixed effects models with adjustment for baseline values, study site, treatment at baseline, and age gave intervention effect estimates (intervention minus control) at 12 weeks of 129 (95% confidence interval 83 to 176) for

metres walked in 12 minutes, 182 (75 to 289) for minutes of moderate intensity activity reported in a week, 2.6 (1.6 to 3.7) for shoulder mobility, 2.5 (1.0 to 3.9) for breast cancer specific subscale of quality of life, and 4.0 (1.8 to 6.3) for positive mood. No significant effect was seen for general quality of life (FACT-G), which was the primary outcome. At the six month follow-up, most of these effects were maintained and an intervention effect for breast cancer specific quality of life emerged. No adverse effects were noted.

Conclusion Supervised group exercise provided functional and psychological benefit after a 12 week intervention and six months later. Clinicians should encourage activity for their patients. Policy makers should consider the inclusion of exercise opportunities in cancer rehabilitation services.

Trial registration Current controlled trials ISRCTN12587864.

INTRODUCTION

Treatments for cancer can result in significant reductions in many different quality of life outcomes.¹ Current programmes in cancer rehabilitation are mainly based on psychotherapy or social support. Such