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

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CRD summary
This well-conducted review evaluated the effects of adjunctive antithyroid drugs on treatment failure, hypothyroidism and adverse events following radioiodine treatment in adults with hyperthyroidism. The authors concluded that antithyroid drugs can increase treatment failure and reduce hypothyroidism when administered in the week before or after radioiodine treatment, respectively. Despite poor study quality, the conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of adjunctive antithyroid drugs on the risks of treatment failure, hypothyroidism and adverse events following radioiodine treatment.

Searching
MEDLINE and EMBASE (both from inception to August 2006) and the Cochrane CENTRAL Register (Issue 1, 2006) were searched for relevant studies; the search terms were reported. The websites www.controlled-trials.com and www.update-software.com/national were also searched (in August 2006). The reference lists of identified articles, narrative reviews and recently published editorials were also consulted. Experts were contacted for unpublished trials.

Study selection
Study designs of evaluations included in the review
Randomised and non-randomised studies were eligible for inclusion. Only randomised controlled trials (RCTs) with a minimum follow-up of 6 months were eligible for inclusion in the meta-analysis. The majority of the included trials were followed up for 1 year.

Specific interventions included in the review
Studies of radioiodine treatment with adjunctive antithyroid drugs were eligible for inclusion. Studies were excluded if they delivered different target doses of radioiodine to compensate for a potential effect of the antithyroid drug. The antithyroid drugs included in the analysis were propylthiouracil (mean dose: 50 to 300 mg/day), carbimazole (20 to 30 mg/day) and methimazole (5 to 30 mg/day); these were given before, at the same time, or before and after radioiodine treatment. The majority of the studies used an adapted uptake of radioiodine; only a few studies used a fixed regimen. Several studies administered additional beta adrenergic blocking agents.

Participants included in the review
Studies of adults with hyperthyroidism were eligible for inclusion. The included studies contained men and women with a mean age range of 35 to 60 years. Some studies included only patients with Grave's disease.

Outcomes assessed in the review
Studies allowing the determination of treatment failure rate (persistent or recurrent hyperthyroidism, or need for further treatment), hypothyroidism, and adverse effects 6 to 12 months after radioiodine treatment were eligible for inclusion. The definition of thyroid status varied across the included studies.

How were decisions on the relevance of primary studies made?
Three investigators independently assessed the eligibility of studies for inclusion in the review. Any disagreements were resolved by consensus.

Assessment of study quality
Three investigators independently assessed the quality of the included studies according to the following: concealment of treatment allocation; completeness of follow-up; blinding of the patients, caregivers and outcome assessors; and the presence of a sample size calculation. Any disagreements were resolved by consensus.

Data extraction
Three investigators independently extracted the data from the included studies. Authors were contacted for additional data where necessary. Summary risk ratios (RRs) and the corresponding 95% confidence intervals (CIs) were calculated for the main outcomes, based on an intention-to-treat analysis. A per-protocol analysis was also conducted for patients with complete follow-up data for treatment failure and hypothyroidism.

Methods of synthesis
How were the studies combined?
The results of the RCTs were pooled in a meta-analysis using a random-effects model. Publication bias was examined in funnel plots and by using Egger's test.

How were differences between studies investigated?
Heterogeneity was assessed using the Cochran Q test, while inconsistency across the trials was measured using the I-squared statistic. Sensitivity analyses were conducted according to the use of different regimens of radioiodine and antithyroid drug treatments, the method of defining thyroid status, and the inclusion of patients with Grave's disease and those with toxic nodular goitre. The correlations between administered radioiodine activity and hypothyroidism rates and treatment success were calculated.

Results of the review
Fourteen RCTs (n=1,306) were included in the meta-analysis. Details of the non-randomised studies were reported in the authors’ discussion and online (Table A).

The quality of the included trials was generally poor, with few reporting adequate methods of randomisation or blinding. However, 97% of the participants completed the follow-up.

Treatment failure.
Adjunctive antithyroid treatment was associated with a higher risk of treatment failure (RR 1.28, 95% CI: 1.07, 1.52, p=0.006) than the control treatment. There was no differential impact between antithyroid drugs. The per-protocol analysis confirmed this finding, as did a sensitivity analysis where the timing of administration was explored. Heterogeneity amongst the study results was low. When 3 small studies were excluded from the analysis, the significance of the risk remained high and publication bias was lowered (Egger's test, p=0.15).

Hypothyroidism.
A reduced risk of hypothyroidism was reported for adjunctive antithyroid treatment compared with control (RR 0.68, 95% CI: 0.53, 0.87, p=0.006). There was no differential impact between antithyroid drugs. The per-protocol analysis revealed a similar trend, as did a sensitivity analysis on the timing of administration. Heterogeneity amongst the treatment effects was considered low to moderate. When the 3 smallest studies were excluded from the analysis, there was a similar significant reduction in risk and publication bias was also lowered (Egger's test p=0.13).

Further sensitivity analysis revealed higher risks of treatment failure associated with fixed radioiodine doses compared with an adaptive regimen when prior antithyroid treatment was given. A high risk of treatment failure and reduced risk of hypothyroidism were reported when high doses compared with lower doses of antithyroid drug were administered after radioiodine. A highly significant correlation was reported between administered radioiodine activity and rates of hypothyroidism (p<0.001) and successful treatment (p<0.001).

Adverse events.
Adverse events associated with the antithyroid drugs were reported to be low (1.8%). These included allergic skin reactions, transient neutropenia, new onset atrial fibrillation and death.

**Authors’ conclusions**
Antithyroid drugs can increase treatment failure rates and reduce rates of hypothyroidism if they are administered in the week before or after radioiodine treatment, respectively.

**CRD commentary**
The review question was clear and the inclusion criteria were specific with regard to the interventions, participants, outcomes and study design. A thorough search strategy was supported by appropriate attempts to reduce language and publication biases. The review process was systematic and transparently conducted, with relevant validity assessment criteria applied to the included studies. Adequate study details were provided and heterogeneity and publication bias were explored in the analysis. Despite the reported low quality of the included studies, the authors’ conclusions are an accurate reflection of the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.
Research: The authors stated that adequately powered randomised trials with long-term follow-up are needed to evaluate the potential superiority of longer discontinuation intervals of different antithyroid drugs to minimise the risks of hyperthyroidism and hypothyroidism. Quality of life and cardiovascular morbidity and mortality should also be recorded.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.