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Antithyroid drug regimens before and after ^{131}I-therapy for hyperthyroidism: evidence-based?

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ABSTRACT

Background: In view of the new national guideline on thyroid dysfunction, the evidence base for current practice as well as the new guideline is assessed with regard to the use of antithyroid drugs (ATDs) before and after radioiodine (^{131}I) therapy.

Methods: In December 2006, we surveyed 16 hospitals by telephone about different aspects of their antithyroid drug regimen: all eight academic centres and eight nonacademic teaching hospitals. The literature was searched for an evidence-based answer to each question in the inquiry.

Results: 13 of 16 hospitals (81%) use antithyroid drugs for pretreatment before ^{131}I. ATDs are discontinued on average four days before ^{131}I or diagnostic scan. However, 27% stop only three days beforehand, which may diminish the effect of ^{131}I. Propylthiouracil (PTU) is also withdrawn four days before ^{131}I, although the literature shows that PTU diminishes the effect of ^{131}I even if it is stopped 15 days beforehand. Resumption of ATDs after ^{131}I to prevent thyrotoxicosis is common practice (81%). One hospital (6%) never restarts ATDs, two (13%) only by indication. Adjunctive treatment consists of combination therapy in 93%, is usually resumed within two days after ^{131}I therapy, and then continued for two to six months. Routine adjunctive treatment is not evidence-based and may be limited to a high-risk subset, especially elderly patients (>70 years) and patients with cardiac comorbidity. Resumption of ATDs within five to seven days after ^{131}I may diminish the effect of ^{131}I.

Conclusion: Antithyroid drug regimens in the Netherlands are heterogeneous. The evidence base of current practice and the new guideline are discussed.

KEYWORDS

Antithyroid drugs, hyperthyroidism, radioiodine therapy

BACKGROUND

In the Netherlands, Graves' hyperthyroidism is initially treated with antithyroid drugs (ATDs). In case of recurrence, radioactive iodine (^{131}I) is usually the preferred definitive treatment. ATDs are often used before and after treatment with ^{131}I for prevention of symptomatic hyperthyroidism. ATDs are withdrawn a few days before ^{131}I therapy, because continuous use during ^{131}I therapy diminishes radioiodine uptake into the thyroid gland by blocking the organification of iodine. This results in a substantial (up to 50%) reduction of the final cure rate, defined as hypothyroidism or euthyroidism 12 months after ^{131}I therapy, based on fixed doses of radioiodine.[1-3]

In most hospitals, resumption of ATDs following ^{131}I therapy is common practice. Usually patients are treated for a period of two to three months after ^{131}I, because it can take six to eight weeks before the effect of ^{131}I becomes noticeable.

Between hospitals, ATD regimens appear to differ substantially, especially regarding the application of pretreatment, the withdrawal period before ^{131}I therapy, resumption after ^{131}I therapy and the time frame of the adjunctive treatment. The issue of a national guideline for treatment of hyperthyroidism, as well as the anticipated heterogeneity in ATD regimes used in the Netherlands, were reasons to audit the current practice. Our purpose is to compare current practice with the new guideline with regard to the use of antithyroid drugs before and after ^{131}I, and to examine to what extent both practice and guideline are evidence-based.

MATERIALS AND METHODS

In December 2006, we surveyed 16 hospitals by telephone: all eight academic centres as well as eight nonacademic

teaching hospitals, each corresponding to a different academic region. The Chief of the Endocrinology Department was asked to answer the following questions:

1. Do you use antithyroid drugs for pretreatment before or as adjunctive treatment after ^{131}I therapy for hyperthyroidism?
2. Which antithyroid drug do you prefer?
3. How long before ^{131}I therapy is methimazole withdrawn?
4. If propylthiouracil (PTU) is used, how long before ^{131}I therapy is it withdrawn?
5. How long before ^{131}I therapy is levothyroxine withdrawn?
6. Are antithyroid drugs resumed after ^{131}I treatment? If yes, when? With or without levothyroxine? What is the time frame of the adjunctive treatment?
7. Does your hospital have its own guideline on this subject?
8. Are you in need of an evidence-based national guideline?

We made use of a standardised questionnaire, which was filled in for each telephone call.

In addition, the literature was searched for evidence-based answers to each question in the inquiry. PubMed was searched using the sensitive search strategy ((methimazole OR thiamazole OR carbimazole OR propylthiouracil OR antithyroid drug*) AND (radioiodine therapy OR radioactive iodine) AND (hyperthyroidism OR hyperthyroidism[mh])), which was limited by the therapy filter in 'clinical queries' and restricted to human and English. Reference lists of the identified studies were hand-searched for relevant publications. The retrieved articles were assessed for quality, resulting in levels of evidence and grades of recommendation.

RESULTS

Results of the inquiry

In 13 of 16 hospitals (81%) pretreatment with ATDs before ^{131}I therapy is common practice. The ATD is discontinued three to 14 days before ^{131}I or diagnostic scan (average 4 to 5 days), but 27% stop three days before ^{131}I. Two hospitals (13%) use a withdrawal period longer than five days. There appear to be large differences between hospitals with regard to the withdrawal period of levothyroxine (from 3 days to 6 weeks, 77% stop less than four weeks before ^{131}I). One hospital does not stop levothyroxine at all before ^{131}I. The withdrawal period used for PTU does not differ from thiamazole. Resumption of ATDs after ^{131}I therapy is standard practice in 13 hospitals (81%). One hospital (6%) never restarts ATDs, two (13%) only by indication. Adjunctive treatment after ^{131}I consists of combination therapy in 93% and is usually resumed within two days after ^{131}I therapy. Thereafter, ATDs are continued for six weeks to six months (very variable, on average four months). Eight hospitals (50%) do not have their own guideline on this subject. Twelve of 16 hospitals (75%) are in need of a national, evidence-based guideline.

Results of literature study

The extensive search in PubMed yielded 22 relevant articles. Four studies examined the influence of the withdrawal period of ATDs on the final outcome of ^{131}I therapy.[4-7] Examined withdrawal periods were 1, 4, 6 and 16 days. Only the studies assessing withdrawal periods of 4, 6 and 16 days before ^{131}I were of sufficient methodological quality. Results show that a withdrawal period of four days is as good as no pretreatment, with regard to the final outcome of ^{131}I. Another study, showing that a withdrawal period of three days is long enough to provide sufficient radioiodine uptake into the thyroid, was not taken into account because the final outcome of ^{131}I was not a study endpoint.[8] A recent meta-analysis suggests that antithyroid drugs increase failure rates of ^{131}I when given in the week before or after ^{131}I therapy, but no firm conclusions are drawn regarding the optimal interruption period of ATDs.[9] Based on the available literature, we conclude that ATDs should be discontinued at least four days prior to ^{131}I, otherwise the cure rate of ^{131}I will be reduced. ^{131}I dose regimens adapted to uptake rather than fixed doses of radioiodine may compensate for this effect. Five studies show that pretreatment with PTU is associated with a significant increase in the failure rate of ^{131}I therapy, even if the drug is discontinued four to 15 days before ^{131}I.[10-14] The failure rate one year after a single dose of radioiodine is twofold when PTU is discontinued four to seven days before ^{131}I, compared with no pretreatment or pretreatment with another antithyroid agent. A possible explanation may be that much higher doses of PTU are needed to achieve euthyroidism, resulting in larger radioprotective effects of PTU compared with thiamazole. However, thus far methimazole and PTU have never been compared head-to-head in a (randomised) clinical trial.

Little evidence is available on the withdrawal period of levothyroxine. Studies examining the effect of continuous use of levothyroxine during ^{131}I therapy on the final cure rate are lacking. For patients it would be much easier if both thiamazole and levothyroxine could be stopped simultaneously. In toxic nodular goitre or toxic adenoma, stopping levothyroxine could even be harmful as this may lead to uptake of ^{131}I in and radiation of healthy parts of the thyroid.

In most hospitals, resumption of ATDs following ^{131}I therapy is common practice. Usually patients are treated for a period of two to three months after ^{131}I, because it can take six to eight weeks before the effect of ^{131}I becomes noticeable. Arguments in favour of this practice include prevention and treatment of symptomatic hyperthyroidism and thyrotoxicosis due to ATD withdrawal or radiation thyroiditis. The question arises if this is really necessary.

A small study shows that short-term increases in thyroid hormone levels occur primarily as a result of discontinuing antithyroid therapy rather than treatment with ^{131}I itself.[15] These results have been proved by two randomised controlled trials.[16,17] The mean increase in free thyroxine (fT4) levels after discontinuation of antithyroid therapy is 50 to 86%.[15,16] Higher levels of thyroid-stimulating hormone (TSH) receptor autoantibodies at diagnosis are associated with increased worsening of thyrotoxicosis after stopping ATD treatment.[16] Free T4 levels peak seven to 14 days after ^{131}I therapy, after which the levels gradually decrease.[17,18] Patients who are not pretreated do not experience an increase, but a 32% decrease in fT4 levels during the first two weeks after iodine treatment.[16] Free T4 always stabilises during the first 30 days after ^{131}I therapy.[17] This period can be well bridged by a β-blocker, for example propranolol. We conclude that, based on the available literature, there is insufficient evidence for routine use of ATDs after ^{131}I for prevention of symptomatic hyperthyroidism. We suggest limiting adjunctive treatment to a subset of patients with a high risk of thyrotoxicosis with clinical implications, especially elderly patients (above 70 years) and patients with cardiac comorbidity.

Several retrospective studies have consistently suggested that ATDs reduce therapeutic efficacy of ^{131}I by their radioprotective properties, resulting in a greater rate of recurrence of hyperthyroidism.[19] This finding is confirmed by a recent meta-analysis.[9] The question is: how can ATDs inhibit the effect of ^{131}I when the radioiodine has already been taken up by the thyroid? The mechanism is not fully understood. *In vitro* studies suggest that ATDs diminish the susceptibility of the thyroid to ionising radiation through their scavenger-like properties (inhibition of the production of hydrogen peroxide), which may hamper the intended cytogenetic damage induced by the ^{131}I radiation.[20,21] When ATDs can be resumed after ^{131}I remains a matter of debate. It is not possible to draw firm conclusions based on the literature. The only randomised study on this subject shows that resumption of methimazole seven days after ^{131}I therapy prevents the early and transient thyrotoxic phase, without interfering with the ultimate therapeutic efficacy of the ^{131}I treatment.[19] Resumption after five days may also be safe. Because studies examining a resumption period of three or four days are lacking, early resumption of ATDs within five days after ^{131}I therapy should not be recommended as this may diminish the effect of ^{131}I.

DISCUSSION

How evidence-based is the new guideline? Our study shows that ATD regimens before and after ^{131}I for Graves' hyperthyroidism are very heterogeneous. The design of the inquiry may have limitations and it is obvious that we restricted our survey to endocrinologists. The results of the inquiry suggest that the new guideline on Thyroid Dysfunction will fulfil an important need. We hope that the guideline also contributes to more uniformity with regard to the use of ATDs around ^{131}I therapy. The guideline pays attention to this subject in chapter II.3.3 (pages 28-29) with the following recommendations:[22] 1) Methimazole is preferred to PTU as pretreatment before ^{131}I. If PTU is used, this should be withdrawn ten days before ^{131}I treatment. 2) Methimazole (and levothyroxine) should be stopped from three days before to three days after ^{131}I therapy. 3) Adjunctive treatment with ATDs is advised for a period of three months after ^{131}I.

The message that PTU should be avoided as much as possible as pretreatment before ^{131}I and, if used, should be stopped longer before ^{131}I therapy than methimazole is important because current compliance to this relatively new evidence is poor. However, it is a matter of debate whether ten days is enough. Two studies show that the cure rate was still significantly reduced when PTU was discontinued 15 to 55 days before ^{131}I therapy.[12,13] Based on the available literature, our advice would be to stop PTU at least two weeks before ^{131}I treatment.

With regard to withdrawal of methimazole before ^{131}I, only a period of four days can be currently supported by good quality evidence. A withdrawal period of three days is advised in the new guideline. At the moment, it is not proven that a withdrawal period of only three days does not diminish the effect of the ^{131}I therapy (without increasing the radioiodine dose). However, evidence that a three-day period is inferior to a four-day period is also lacking.

Evidence from two studies shows that resumption of ATDs seven days after ^{131}I does not reduce the therapeutic efficacy of ^{131}I;[19,23] however a period shorter than five days may diminish the ultimate cure rate. A recent meta-analysis of RCTs shows that use of ATDs in the week before and after ^{131}I is associated with an increased risk of treatment failure.[9]

Furthermore, the benefit of routine adjunctive treatment for a period of three months after ^{131}I, which is common practice in the Netherlands, can be questioned. From a theoretical and practical point of view, this policy is effective for prevention of symptomatic hyperthyroidism. However, evidence from two randomised controlled trials suggests that ATDs after ^{131}I have little additional value. The increase in fT4 occurs primarily as a result of discontinuing antithyroid therapy rather than ^{131}I therapy and peaks within seven to 14 days. The incidence of exaggerated hyperthyroidism including thyroid storm after ^{131}I is only 0.3%.[9] The incidence of new onset atrial fibrillation after ^{131}I is 0.2% with and 0.5% without ATDs.[9] The number needed-to-treat for prevention of thyroid storm or atrial fibrillation would be 333. Instead of routine application of ATDs after ^{131}I, one may consider limiting adjunctive treatment to a subset of patients with a high risk of thyrotoxicosis with clinical implications, especially elderly

patients (>70 years) and patients with cardiac comorbidity. This would be a safe and cost-effective alternative, as most patients can be treated with a β-blocker only. An overview of our recommendations is shown in *table 1*.

Table 1. *Evidence-based recommendations for improvement of antithyroid drug use around ^{131}I therapy for hyperthyroidism (http://www.cebm.net/levels_of_evidence.asp)*

Grades	Recommendations	References
Grade A	Antithyroid drugs should be withdrawn at least 4 days before ^{131}I therapy in order to prevent treatment failure	5-7
Grade B	Pretreatment with propylthiouracil (PTU) diminishes the effectiveness of ^{131}I treatment, even if it is stopped 4 to 15 days before. If used, PTU should be stopped at least 2 weeks before ^{131}I therapy	10,11,13,14
Grade A	Routine adjunctive treatment with antithyroid drugs for prevention of symptomatic hyperthyroidism is not evidence-based	15-17
Grade A	Antithyroid drugs should not be restarted sooner than 7 days after ^{131}I therapy	9,20,22
Grade D	Resumption within 7 days may weaken the effect of ^{131}I, due to anti-oxidative properties and a decrease in thyroid metabolism	19

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