CLINICAL STUDY

Resumption of methimazole after ^{131}I therapy of hyperthyroid diseases: effect on thyroid function and volume evaluated by a randomized clinical trial

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Abstract

Objective: Retrospective studies have indicated that anti-thyroid drugs (ATD) might possess a radioprotective effect, leading to a higher rate of recurrence of hyperthyroidism after iodine-131 (^{131}I) therapy.
Design: A randomized clinical trial was performed to clarify whether resumption of methimazole after ^{131}I influences the final outcome of this treatment.
Methods: We assigned 149 patients with Graves' disease or a toxic nodular goitre to groups either to resume ($+$ATD) or not to resume ($-$ATD) methimazole 7 days after ^{131}I. Before ^{131}I therapy, all patients were rendered euthyroid by methimazole, which was discontinued 4 days before the ^{131}I therapy.
Results: During the follow-up period of 12 months, 13 patients developed hypothyroidism, 42 were euthyroid, and 18 had recurrence of hyperthyroidism in the $+$ATD group; the respective numbers in the $-$ATD group were 16, 42 and 18 ($P = 0.88$). At 3 weeks after ^{131}I therapy, the serum free-thyroxine index was slightly decreased (by 5.7%; 95% confidence interval (CI) -15.5 to 5.4%) in the $+$ATD group, in contrast to an increase of 35.9% (95% CI 18.8 to 55.5%) in the $-$ATD group ($P < 0.001$ between groups). In the subgroup that remained euthyroid during follow-up, thyroid volume reduction, assessed by ultrasonography, was smaller in the $+$ATD group [38.7% (95% CI 33.3 to 44.1%)] than in the $-$ATD group [48.6% (95% CI: 41.5–55.6%)] ($P < 0.05$).
Conclusion: No radioprotective effect could be demonstrated, with regard to final thyroid function, for the resumpton of methimazole 7 days after ^{131}I therapy. Although resumption of methimazole slightly reduced the magnitude of shrinkage of the goitre obtained by ^{131}I, the prevention of a temporary thyrotoxicosis in the early period after radiation favours this regimen.

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Introduction

For the last half century, radioiodine (^{131}I) therapy has been widely used as the definitive treatment of patients with hyperthyroidism. Approximately 30% of physicians prefer to render their patients euthyroid by prescribing anti-thyroid drugs (ATDs) before ^{131}I therapy, whereas 40% use ATDs after the therapy (1). However, the use of ATDs in conjunction with ^{131}I treatment may not be without problems. ATDs at physiological concentrations in cell cultures appear to have scavenger-like properties, inhibiting the production of hydrogen peroxide (2), which may hamper the intended cytogenetic damage induced by the ^{131}I radiation. Whether this observation has any clinical relevance is unknown. Other factors may also be of importance. Administration of ATDs before ^{131}I therapy does not seem to influence the iodine kinetics (3), but it is a matter of speculation whether ATDs diminish the susceptibility to ionizing radiation through a decrease in thyroid metabolism. Regardless of the mechanism that might be responsible, several retrospective studies have consistently suggested that ATDs possess radioprotective properties, thereby attenuating the effect of ^{131}I, with a subsequently greater rate of recurrence of hyperthyroidism. This applies to the periods both before (4–13) and after (14–18) ^{131}I therapy. However, the possible radioprotective role of ATDs remains controversial (19), and was brought strongly into question recently by the findings of two randomized trials, in which methimazole pre-treatment was shown not to affect the outcome of the ^{131}I therapy (20, 21).

The aim of this randomized clinical trial was to elucidate the role of resumption of methimazole after ^{131}I treatment for hyperthyroidism.

Materials and methods

Patients and design

We enrolled patients with toxic nodular goitre or recurrent Graves' disease, who were referred for ^{131}I

treatment at our institution. No patient had previously received ^{131}I. Before ^{131}I therapy, all patients were treated with methimazole. The dose of methimazole was adjusted to ensure a stable euthyroidism for at least 3 months before the ^{131}I treatment. All patients were instructed to stop the medication 4 days before undergoing radioiodine therapy. At the time of inclusion in the study, the patients were allocated randomly (computer-generated numbers in closed envelopes) to groups either to receive no methimazole ($-$ATD) after ^{131}I, or to resume the pre-treatment dose of methimazole 7 days after the ^{131}I therapy ($+$ATD). In the latter case, the medication was subsequently discontinued, at the earliest, 1 month after ^{131}I, providing biochemical euthyroidism. The two ATD regimens are summarized in Fig. 1. Thyroid function was monitored after 3, 6 and 12 weeks, and thereafter every 3 months for a follow-up period of 1 year. If biochemical evidence of thyrotoxicosis was observed in the early period after ^{131}I, β-blockers were commenced, provided that the patient had symptoms of thyrotoxicosis. If hyperthyroidism persisted beyond 6 weeks, methimazole was reinstituted ($-$ATD group) or maintained ($+$ATD group), and this medication was subsequently tapered during the follow-up period. If this was not successful, a second dose of ^{131}I was eventually administered, at the earliest, 9 months after the initial therapy. Hypothyroidism was treated with levothyroxine (L-T$_4$). If a low dose of L-T$_4$ was required, a trial of discontinuation was made within the follow-up period, to ensure that the hypothyroidism was not transient. At the end of follow-up, the patients were classified as being hypothyroid, euthyroid or hyperthyroid according to their thyroid function resulting from the initial ^{131}I treatment (e.g. a patient developing myxoedema after a second ^{131}I

administration because of failure of the initial ^{131}I dose was classified as having recurrence of hyperthyroidism). Euthyroidism was defined as serum T$_4$ and tri-iodothyronine (T$_3$) indices within the normal range; hypothyroidism was defined as serum thyroid-stimulating hormone (TSH) above the normal range and serum T$_4$ index below the normal range; hyperthyroidism was defined as serum TSH below the normal range and serum T$_4$ or T$_3$ indices above the normal range.

The study was approved by the Ethics Committee of the county of Funen, Denmark (journal no. 95/10). All patients provided signed informed consent.

Assays, imaging and ^{131}I therapy

Total serum T$_4$ (normal range $65-135$ nmol/l) and T$_3$ (normal range $1.00-2.10$ nmol/l) were measured by RIA (Diagnostic Products Corp., Los Angeles, CA, USA and Johnson & Johnson, Amersham, UK, respectively). Serum TSH (normal range $0.30-4.0$ mU/l) was determined by DELFIA (Wallac OY, Turku, Finland). Free T$_4$ and free T$_3$ indices were calculated by multiplying the total values by the percent T$_3$ resin uptake. Serum anti-thyroid peroxidase (anti-TPO) antibodies were determined at baseline and at the end of follow-up by the RIA DYNO test (Brahms Diagnostics, Berlin, Germany; normal range <200 U/l). Thyroid ^{99m}technetium scintigraphy was performed at baseline on a high resolution gamma camera equipment. Ultrasound, including a morphological imaging and a planimetric volume estimation, was performed at baseline and 1 year after ^{131}I, by trained endocrinologists. This method for determination of thyroid volume has intra- and interobserver coefficients of variation of 5% and 7% respectively (22). Classification as Graves' or
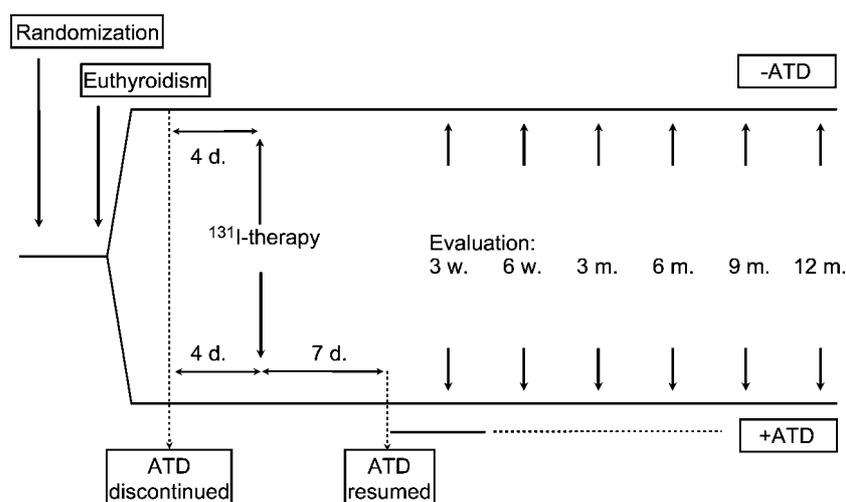
Figure 1 Study design. Until 4 days before the ^{131}I therapy, all patients were treated with methimazole. In the $+$ATD group, methimazole treatment was resumed 7 days after the ^{131}I therapy. Renewed withdrawal of methimazole in that group was performed when the thyroid function test revealed euthyroidism, at the earliest, 1 month after treatment. In the $-$ATD group, methimazole were resumed only if hyperthyroidism persisted beyond 6 weeks after treatment. d, days; w, weeks; m, months.

nodular thyroid disease was based on the clinical presentation, the results of the imaging methods and a determination of serum TSH-receptor antibodies (Medi-Lab, Copenhagen, Denmark).

^{131}I was given routinely as a single oral dose on an outpatient basis. The amount of radioactivity was based solely on the size of the gland estimated by ultrasound. The administered activities were 200 MBq for glands <30 ml, 400 MBq for glands >30 ml and <60 ml, and 600 MBq if the size was in excess of 60 ml. However, to ensure that the iodine pool was equal in both groups, a 24-h ^{131}I-uptake measurement was performed at random in a subset of patients ($n = 85$).

Statistical analysis

Anticipating a cure rate (euthyroidism or hypothyroidism) of 60% in one of the randomization arms, we calculated that a sample size of 72 per group would provide 90% power to ensure detection of a difference in cure rate of at least 25% between the two arms. Baseline data are presented as mean±S.D., or median and range if the data were not normally distributed. χ^2-test, one-way analysis of variance (ANOVA) and Mann–Whitney test (if appropriate) were used to compare baseline characteristics, and χ^2-test and one-way ANOVA were used in analyses of differences in outcome. McNemar's test was used to analyse whether a shift had occurred in the status of thyroid autoantibodies (negative or positive titre). Measurement errors are given as 95% confidence intervals (CI). A stepwise multinomial logistic regression analysis was used for testing correlations. Logarithmic data transformation was performed in the case of skewed distribution of data, or if calculations involved ratios. A P value <0.05 was considered statistically significant.

Results

During a period of 3.5 years, a total of 434 hyperthyroid patients were referred for ^{131}I treatment (Fig. 2). Two hundred and sixty-seven individuals were not eligible for inclusion for various reasons, e.g. current treatment with propylthiouracil (PTU), large or partly intrathoracic goitre, allergic reaction to methimazole, physical or psychiatric disabilities, or anticipation of practical difficulties in completion of follow-up. Fifteen patients declined to participate in the trial. Another three patients were secondarily excluded shortly after random allocation to groups and before ^{131}I therapy, because they regretted their commitment. Of the remaining 149 patients who were included, four individuals died of unrelated causes, and another two patients were lost to complete follow-up. The thyroid status of these patients at the time of dropout is included in the analysis. The patients in the two

randomization arms did not differ in most baseline characteristics (Table 1). The median age of the study population was 59 years (range 23–90 years), but in the +ATD group the patients were, on average, 4.8 years older. Patients with Graves' disease were younger than those with toxic nodular disease (49.8±12.1 years and 63.1±11.3 years, respectively, $P < 0.001$). Serum TSH before ^{131}I therapy was below the reference interval in 58.1% of the patients and did not differ between the −ATD and +ATD groups. The median dose of methimazole was 5.0 mg (range 2.5–20 mg), and the median ^{131}I activity administered was 400 MBq (range 200–600 MBq; mean 395±154 MBq), with insignificant between-group differences of both variables. According to the routine recommended in our department, glucocorticoids were used prophylactically in 18 patients in order to prevent a worsening of pre-existing Graves' ophthalmopathy. Forty-six patients suffered from Graves' disease, 22 had a solitary toxic nodule, and 81 were classified as having a multinodular toxic goitre. The median time for discontinuation of the medication after ^{131}I in the +ATD group was 6 weeks (range 4–44 weeks).

At the end of the 1-year follow-up period, 84 patients were classified as euthyroid, 29 developed permanent hypothyroidism, and the remaining 36 experienced recurrence of hyperthyroidism (Table 2). The figures in each of the two randomization arms were nearly similar, with no indication of any influence of methimazole on the efficacy of ^{131}I therapy ($P = 0.88$). This also held true when the outcome was evaluated separately for type of disease (Table 2). Patients with a multinodular gland were usually (74% of the cases) rendered euthyroid, whereas this was achieved in only 33% of patients with Graves' disease. Patients with Graves' disease significantly more often experienced permanent hypothyroidism or recurrence, respectively, than did the patients with non-autoimmune hyperthyroid diseases. This relationship became less obvious according to a multiple regression model taking into account a number of factors (including ATD) with a potential impact on the final effect of ^{131}I therapy (Table 3). In the case of permanent hypothyroidism, a small thyroid volume ($P = 0.014$) and young age ($P = 0.013$) were independent variables, whereas presence of Graves' disease was the only risk factor with regard to recurrence ($P = 0.015$) (Table 3). Sex, presence of pretreatment anti-TPO antibodies and the TSH concentration were not found to have any independent roles, as was the case with ATD. In none of the groups was the status of anti-TPO antibodies significantly altered by the ^{131}I therapy (conversion of the serum titre from negative to positive or *vice versa*).

Marked differences in the serum concentrations of T_4 and T_3 were seen in the period early after treatment (Fig. 3). In the +ATD group, the serum free-T_4 index decreased by −5.7% (95% CI −15.5 to +5.4%) and −10.6% (CI 95% −21.3 to +1.5%) respectively, at
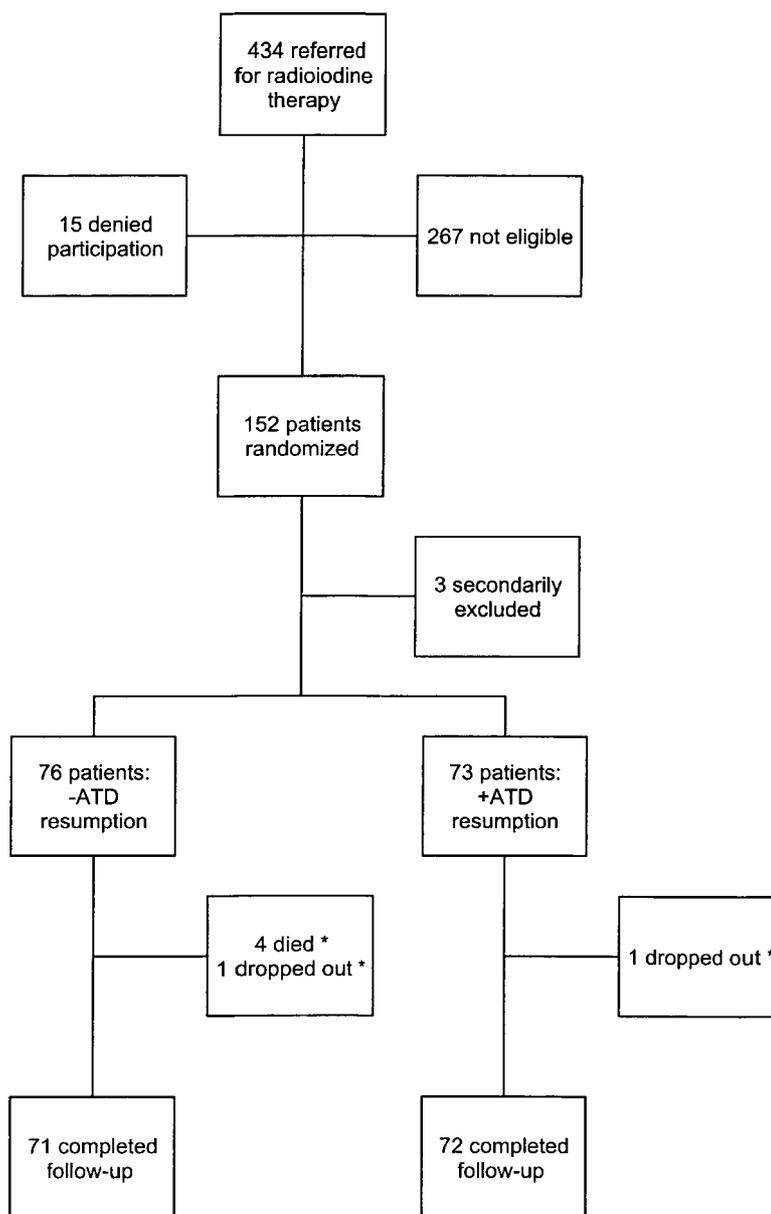
Figure 2 Trial profile. *Status of thyroid function at dropout is included in the analysis.

3 and 6 weeks after ^{131}I therapy. In contrast, in the $-$ATD group the same variable increased by $+35.9\%$ (95% CI $+18.8$ to $+55.5\%$) and $+30.1\%$ (95% CI $+14.1$ to $+49.7\%$) respectively at these times ($P < 0.001$; Fig. 3). A similar pattern, although slightly blunted, was found for the serum free-T_3 index (Fig. 3). In the $-$ATD group, 26.4% of the patients attained thyroid hormone concentrations above the normal range, compared with 11.1% in the $+$ATD group, which resulted in a more frequent use of β-blockade in the former group (eight patients and one patient, $P < 0.02$). As persisting hyperthyroidism triggered an intervention in terms of reinstitution of

methimazole and, eventually, a second dose of ^{131}I, no further analysis of this aspect of the ^{131}I therapy was made beyond these first 6 weeks.

For the euthyroid subgroup, being without influence from either L-T_4 or a second dose of ^{131}I, the reduction in thyroid volume was 43.4% (95% CI 39.0 to 47.9%). There was, however, a significantly lower reduction (38.7%; 95% CI 33.3 to 44.1%) in the $+$ATD group, compared with that in the $-$ATD group (48.6%; 95% CI 41.5 to 55.6%) ($P < 0.05$; Table 2). Stratifying for type of disease, this difference also held for the patients with multinodular toxic goitre, but the numbers of patients with Graves' disease and a solitary toxic

Table 1 Group characteristics.

Variable	ATD resumed ($n = 73$)	ATD not resumed ($n = 76$)	P
Age (years)	61.6±12.1	56.8±13.8	<0.05
Sex (female/male)	58/15	66/10	ns
Classification			
Graves' disease	17	29	
AFTN	10	12	
MNTG	46	35	ns
Previous thyroidectomy	4	4	ns
Thyroid volume (ml)	45 (7–140)	41 (14–125)	ns
24-h ^{131}I uptake (%)*	65.2±15.7	65.3±12.1	ns
^{131}I activity administered (MBq)	400 (200–600)	400 (200–600)	ns
Presence of anti-TPO antibodies	20	25	ns
Serum TSH (mU/l)	0.05 (<0.01–9.12)	0.09 (<0.01–4.96)	ns
Serum free T_3 index (nmol/l)	1.79±0.72	1.82±0.75	ns
Serum free T_4 index (nmol/l)	96.7±46.2	90.6±33.0	ns
Prophylactic steroids	5	13	ns

Values are number of patients, mean±S.D. or median (range).
AFTN, autonomously functioning toxic nodule; MNTG, multinodular toxic goitre.
*Measurement of uptake was performed at random in 85 patients to ensure congruence of this variable between the groups.

Table 2 Thyroid function 1 year after ^{131}I therapy, according to randomization in 149 patients, and reduction in thyroid volume at follow-up for 77 euthyroid patients.

	ATD resumed	ATD not resumed	P
Thyroid function (H/E/R)			
All glands ($n = 149$)	13/42/18	16/42/18	ns
Graves' disease ($n = 46$)	6/4/7	9/11/9	ns
AFTN ($n = 22$)	1/4/5	3/5/4	ns
MNTG ($n = 81$)	6/34/6	4/26/5	ns
Thyroid volume reduction (%)			
All glands ($n = 77$)	38.7 (33.3 to 44.1)	48.6 (41.5 to 55.6)	<0.05
Graves' disease ($n = 13$)	55.4 (41.7 to 69.1)	61.2 (51.4 to 71.0)	ns
AFTN ($n = 8$)	47.8 (20.1 to 75.5)	27.9 (0.0 to 83.7)	ns
MNTG ($n = 56$)	36.1 (30.3 to 41.9)	46.7 (38.7 to 54.6)	<0.05

Values are numbers of patients or mean (95% confidence interval).
H, hypothyroidism; E, euthyroidism; R, recurrence; AFTN, autonomously functioning toxic nodule; MNTG, multinodular toxic goitre.

Table 3 Relevant variables included in the regression analysis for prediction of either recurrence or hypothyroidism 1 year after ^{131}I therapy.

Variable	Recurrence ($n = 36$)	Hypothyroidism ($n = 29$)
ATD resumption	ns	ns
Sex	ns	ns
Graves' disease	P = 0.015	ns
Presence of anti-TPO Ab	ns	ns
Small thyroid volume	ns	P = 0.014
Young age	ns	P = 0.013
TSH concentration before ^{131}I	ns	ns

AB, antibody.

nodule were too small to allow any valid conclusion to be drawn (Table 2). Possible confounding factors, such as the pretreatment concentrations of serum TSH and anti-TPO antibodies, and age, did not affect this relationship between resumption of methimazole and reduction in thyroid volume.

Discussion

This study enrolling 149 patients with hyperthyroid diseases is the first randomized trial to evaluate the impact of the resumption of methimazole 7 days after ^{131}I therapy, and it is one of very few randomized studies addressing the issue of radioprotective properties of ATD. Recent randomized trials (20, 21) have documented – in sharp contrast to what was indicated by previous retrospective studies (4–13) – that pre-treating hyperthyroid patients with methimazole before ^{131}I therapy does not interfere with the final cure rate. In 1988, Velkeniers *et al.* (14) reported that treatment failure occurred almost five times more often if ATDs were resumed after ^{131}I therapy of hyperthyroidism. Subsequently, the findings of other studies (15–17) supported the view that the use of ATDs in the period after ^{131}I treatment reduced the cure rate from the therapy, in some cases associated with a blunted ^{131}I-induced increase in the titres of thyroid autoantibodies (17). However, all those studies

(a)

(b)
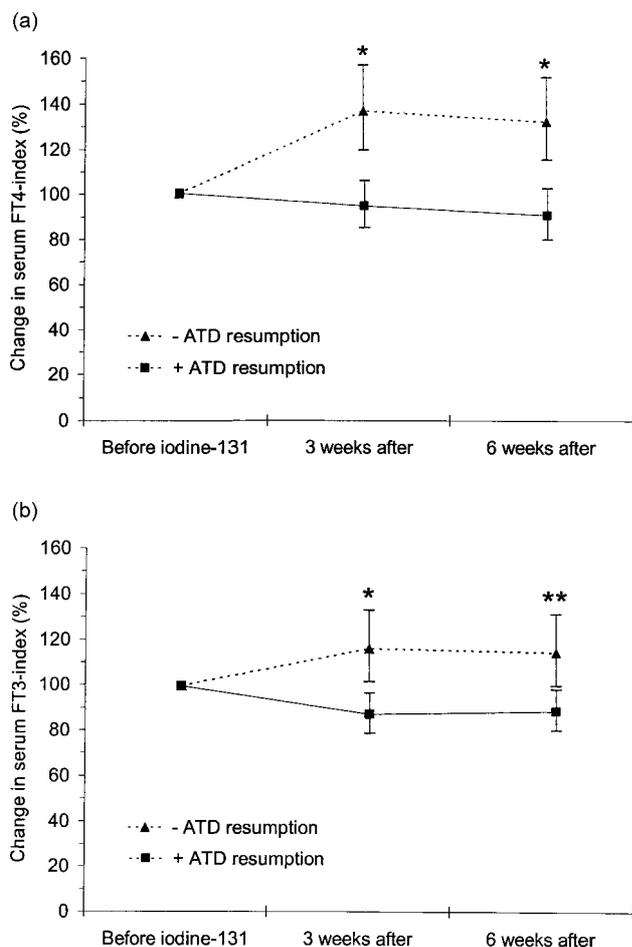
Figure 3 Percent changes in (a) serum free thyroxine (FT$_4$) index and (b) serum free tri-iodothyronine (FT$_3$) index in the early period after ^{131}I treatment. Pretreatment values are given as 100%. Bars represent 95% confidence intervals. *$P < 0.001$, **$P = 0.004$ comparing the $-$ATD ($n = 76$) and $+$ATD groups ($n = 73$).

(14–17) suffered from the drawbacks unavoidable in retrospective designs. In the randomized study by Kung *et al.* (18), also dealing with the impact of methimazole in the period after ^{131}I therapy, a lower incidence of early permanent hypothyroidism, but not of recurrence, was demonstrated after ^{131}I therapy of patients with Graves' disease. In that study (18), patients were not pre-treated with ATDs, and methimazole was instituted 4 days after ^{131}I therapy, followed by a block-replacement regimen, which included a larger dose of methimazole than was used in the present study, in addition to L-T$_4$.

The two regimens applied in our study are widely used routinely at institutions treating patients with hyperthyroidism, and we could not demonstrate any effect on the final thyroid function caused by the resumption of methimazole 7 days after ^{131}I treatment. It remains an open question whether the outcome would have been different if the delay between the administration of ^{131}I and the resumption of methimazole

had been shorter. Our findings are further underscored by the outcome of the multivariate analysis taking into account the type of disease, thyroid volume, anti-TPO antibodies, TSH concentration at treatment, age and sex. In such an analysis, correction is made for any bias that might have occurred despite randomization. Only the presence of Graves' disease was related to recurrence of hyperthyroidism. Young age *per se* did not prove to be an independent factor, as has been shown in other studies (12, 13), but this finding probably reflects the fact that patients with Graves' disease were younger than those with thyroid nodular diseases.

Although a 24-h uptake measurement was performed to ensure congruence between the two randomization groups, dosage of the ^{131}I therapy was calculated according to a simplified algorithm taking into account only the thyroid volume (estimated by ultrasound). At several institutions, including ours, elaborate algorithms for dose calculation have been disregarded in favour of a more simple approach. This is justified by studies showing that calculated doses do not carry any advantages over fixed doses (23–25). Detrimental to any algorithm that includes a 24-h uptake is the great variation in ^{131}I uptake and turnover over short periods of time (26). In addition, the correlation between the intended and the actual dose delivered to the thyroid is highly variable, with a mean coefficient of variation of 45% (27). It is therefore not surprising that susceptibility of the thyroid to a wide range of ^{131}I radiation shows huge individual variations (28).

Similarly to other recent studies (12, 29, 30) performed in order to evaluate the efficacy of ^{131}I therapy, we included patients with both autoimmune (Graves' disease) and non-autoimmune hyperthyroid diseases. Our finding of no radioprotection of methimazole, among patients with either Graves' disease or toxic nodular goitre, is in contrast to the findings by Körber *et al.* (30). In their study, continuation of ATD therapy until at least 14 days after ^{131}I therapy resulted in a lower success rate, but only among patients with toxic nodular disease. However, patients were not allocated randomly to groups, and those receiving ATDs had greater serum concentrations of TSH, which was not the case in our study. In non-randomized studies, patients who continue to take ATDs during and after ^{131}I therapy are prone to suffer from a more aggressive disease, with a greater degree of hyperthyroidism. This is obviously a source of bias that cannot easily be corrected for in a multivariate analysis. Thus, on the basis of our own results, we find no reason to believe that any radioprotective effect from methimazole should act preferentially against certain subtypes of hyperthyroid disease, provided the TSH concentration is taken into account. One study (7) – also non-randomized – has indicated that PTU could have a greater radioprotective effect, if any such effect were present at all, than methimazole. For this reason we excluded

patients pre-treated with PTU. Whether this drug has any radioprotective potential when tested in a randomized design remains an open question.

Although the resumption of methimazole did not affect long-term thyroid function, some impact was found as regards thyroid volume. The ultrasound planimetric method used in this study is a very precise method for estimation of thyroid volume (22). The overall 43% reduction in thyroid volume, a little less for nodular glands and more for diffuse glands, corresponds well to the results from earlier studies (31–33). However, in patients who resumed methimazole, ^{131}I treatment resulted in a significantly smaller reduction in thyroid volume. An independency of the effects of ^{131}I on thyroid size and function has been described previously (31). The difference was detectable only in multinodular glands showing a reduction in thyroid volume of 36% if methimazole was resumed, compared with 47% if methimazole was not resumed. Our finding seems to be of only minor clinical relevance in most patients; however, should the hyperthyroidism be caused by a large symptomatic compressive thyroid gland, methimazole should probably not be resumed after ^{131}I therapy, in order to optimize the reduction in goitre size.

The most pronounced difference between the two regimens used in this study was seen in the thyroid hormone concentrations early after the ^{131}I therapy. In patients randomly assigned to resumption of methimazole, thyroid function was very stable after the ^{131}I therapy and fluctuations in the thyroid hormone concentrations were generally avoided. In contrast, the serum T_4 concentration increased by a mean of 36% at 3 weeks if methimazole was not resumed, which resulted in more patients having symptoms of thyrotoxicosis. Radiation thyroiditis – defined as thyroid tenderness, increased sedimentation rate and thyrotoxicosis – is seen in a small percentage of patients after ^{131}I therapy (34). To avoid 'dumping' of thyroid hormones into the circulation and the rare precipitation of 'thyroid storm', guidelines (35) recommend pretreatment with ATDs before ^{131}I therapy, to deplete the thyroid hormone stores. The importance of thyroid peroxidase suppression during ^{131}I therapy has been elucidated by Andrade *et al.* (36) and Burch *et al.* (37). From these important studies, both randomized, it is clear that ^{131}I therapy in untreated and thyrotoxic patients with Graves' disease does not lead to any further secretion of the thyroid hormones. In contrast, in patients rendered euthyroid by ATDs, the serum hormone concentrations increase by 50–100% (but from a euthyroid level) if the medication is discontinued a few days before ^{131}I therapy (36, 37). Although ^{131}I therapy *per se* apparently does not cause exacerbation of the thyrotoxicosis, the present results clearly show that, once methimazole has been instituted in hyperthyroid patients, this restraint upon the thyroid hormone production is important to carry

through until the destructive effect of the ^{131}I therapy ensues. By resumption of methimazole after ^{131}I therapy, the early and transient thyrotoxic phase can be avoided, and although such strategy seems to attenuate the goitre shrinkage to a minor degree in patients with multinodular glands, it does not interfere with the final outcome as regards thyroid function.

Acknowledgements

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