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Original article

Factors associated with recurrence of hyperthyroidism after ^{131}I treatment: the inadvertent influence of antithyroid drug administration after ^{131}I treatment of hyperthyroidism

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Abstract

The aim of this study was to identify factors associated with recurrence of hyperthyroidism after ^{131}I treatment, in particular to examine if post-treatment administration of antithyroid drugs (ATD) is associated with an increased risk of recurrence. The study population comprised 210 consecutive hyperthyroid patients referred for ^{131}I treatment and followed one year hereafter. The patients were included in a previously published randomized clinical trial comparing the effect of fixed versus calculated ^{131}I doses on the outcome. The association of variables describing the patients and the treatment with the outcome was examined. Single variables were compared using the Mann-Whitney test or Fisher's exact probability test and combinations of variables were assessed using logistic regression analysis. Recurrence of hyperthyroidism occurred in 13% of the patients who did not receive ATD after ^{131}I treatment and in 37% of the patients who did receive ATD after ^{131}I treatment. The only independent variables significantly related to the recurrence of hyperthyroidism were resumption of ATD after ^{131}I treatment of hyperthyroidism ($p = 0.0007$), higher thyroid volume ($p = 0.004$), lower ^{131}I dose ($p = 0.001$), and higher pretreatment FT3I ($p = 0.007$). Future treatment regimes should take this into consideration and avoid the administration of ATD after ^{131}I treatment.

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Introduction

^{131}I has become one of the most commonly used agents for the treatment of hyperthyroidism [1-5]. The ideal dose, would be that causing just enough damage to the thyroid gland to reduce thyroid function to normal without causing hypothyroidism. Antithyroid drugs (ATD) have been administered before and after ^{131}I treatment in order to restore euthyroidism as quickly as possible. Nygaard et al. [6] have shown that pretreatment with ATD did not reduce the incidence of early hypothyroidism in ^{131}I treated patients with Graves' disease. Likewise, Aro et al. [7] have previously shown that the administration of carbimazole prior to and after ^{131}I treatment of hyperthyroidism did not influence the incidence of hypothyroidism when

compared to propranolol as adjunctive therapy. The purpose of pretreatment with ATD is to deplete thyroid hormone stores before ^{131}I is given, and thereby avoid the danger of exacerbating hyperthyroidism during the acute phase of radiation thyroiditis. Some physicians prefer to let their patients resume ATD after ^{131}I treatment, presumably in order to maintain euthyroidism, and there are various opinions as to the influence on recurrence or persistence of hyperthyroidism and incidence of early and late hypothyroidism [8-13].

The aim of the present study was to assess which variables were associated with recurrence after ^{131}I treatment. In particular we wished to examine whether ATD administered after ^{131}I treatment have an independent influence on recurrence of hyperthyroidism.

Materials and methods

The study population consisted of 221 consecutive hyperthyroid patients referred for ^{131}I treatment. The diagnosis of hyperthyroidism was based on clinical symptoms and paraclinical data. Inclusion criteria: 1) Age > 18 years; 2) No pregnant or lactating women; 3) No previous ^{131}I treatment; 4) No previous thyroidectomy; 5) No clinically evident thyroid associated ophthalmopathy. Patients were recruited from october 1990 through may 1993. The patients were randomly allocated [14] to one of two dosage schemes with ^{131}I, previously demonstrated to be equal with regard to outcome: A fixed dose regime comprising doses of 185, 370, or 555 MBq based on gland size assessment by palpation only or a calculated ^{131}I dose based on type of thyroid gland (diffuse, multinodular, solitary adenoma), an accurate thyroid volume measurement, and a 24-hour ^{131}I uptake determination [15].

Before treatment with ^{131}I a ^{99m}Tc-pertechnetate scintigram, a 24 hour uptake of ^{131}I, and an ultrasonic estimation of thyroid volume were performed. The patients were followed, before treatment, and after 1, 2, 3, 6, 9, and 12 months with measurements of serum T4, T3 and T3 resin uptake test, and a serum free T4 index (FT4I) (serum T4 multiplied by the T3 resin uptake test), FT3I, and TSH [15].

Four patients died for reasons unrelated to hyper-thyroidism and seven were lost during the follow-up period. The remaining 210 patients were included in the analysis (Tab. I).

The patients were followed for 12 months after ^{131}I treatment. In the final classification 12 months after the initial ^{131}I dose the patients could be classified as 1) *euthyroid* - normal FT3I and FT4I with low or normal TSH values without thyroid medication; 2) *hyperthyroid* - FT4I and/or FT3I values significantly elevated 1 month or more after withdrawal of antithyroid drugs. (A second ^{131}I dose was not given until 6 months after the initial ^{131}I treatment); 3) *hypothyroid* – subnormal thyroid function, that is low FT4I and elevated values of TSH, or euthyroid on thyroxine substitution. Transient hypothyroidism (thyroxine replacement therapy could be withdrawn within 6 months of ^{131}I treatment) was excluded.

ATD were administered prior to ^{131}I treatment either by us or by the referring doctor to establish euthyroidism as quick as possible. Thionamides were withdrawn 4 days before ^{131}I treatment and ATD were resumed 7 days after ^{131}I treatment for a period of 3 weeks.

Tab. I.
Data for 210 hyperthyroid patients (median and range for quantitative variables, number and percent for qualitative variables).

Number	210	
Male	24	(11.4%)
Female	186	(88.6%)
Age (years)	62	(26-85)
ATD prior to ^{131}I treatment	187	(89.0%)
ATD after ^{131}I treatment	163	(77.6%)
Diffuse glands	60	(28.6%)
Multinodular glands	115	(54.8%)
Hot adenomas	35	(16.7%)
Thyroid volume (ml)	42.5	(8-282)
24 h radioactive iodine uptake (%)	62.5	(22-91)
131I dose (MBq)	298	(37-740)
Fixed dose regime	104	(49.5%)
Calculated dose regime	106	(50.5%)
Endpoints:		
Recurrence (hyperthyroidism)	67	(31.9%)
Euthyroidism	123	(58.6%)
Hypothyroidism	20	(9.5%)

Statistical analysis

Of the 210 patients studied 67 developed recurrence (hyperthyroidism) while 143 did not. Each of the descriptive variables characterizing the patients were compared between these two groups using Mann-Whitney ranksum test (quantitative variables) or Fisher's exact probability test (quali-

tative variables). The combined association of more descriptive variables with recurrence was studied using logistic regression analysis[16]. The logistic regression model is as follows:

$Y = b_0 + b_1 \times z_1 + \ldots . + b_p \times z_p$,

where Y is the logit, i.e. $Y = \log_e(P/(1 - P))$ where P is the probability of developing recurrence (i.e. $P = e^Y/(1 + e^Y)$), b_0 is a constant, $z_1 - z_p$ are the scorings of the p variables, $b_1 - b_p$ are the regression coefficients corresponding to each of the variables $z_1 - z_p$.

All descriptive variables were considered for inclusion in the logistic regression model. To fulfill the model assumption of linearity and to give the best fit in the model, a logarithmic transformation of some highly skewed variables had to be used. The final model was obtained using backward elimination of insignificant variables ($p > 0.05$). The following variables were excluded: Gender, age, type of thyroid gland, 24-hour ^{131}I uptake, TSH, FT4I, ATD prior to ^{131}I treatment, type of ATD, duration of ATD, and dosage regimes (Tab. II).

Results

Recurrence of hyperthyroidism occurred in 67 (32%) of the 210 patients.

By univariate analysis the following variables were associated with recurrence: ATD after ^{131}I treatment, diffuse glands, higher 24-hour ^{131}I uptake, higher pretreatment FT3I, longer duration of pretreatment with ATD, and more frequent use of carbimazole before and after the ^{131}I treatment.

In multivariate analysis (Tab. II) the following variables had significant independent associations with recurrence: lower ^{131}I dose ($p = 0.001$), higher thyroid volume ($p = 0.004$), higher pretreatment FT3I ($p = 0.007$), and ATD after ^{131}I treatment ($p = 0.0007$). Among the 47 patients who did not receive ATD after ^{131}I treatment 6 (13%) had recurrence of hyperthyroidism, whereas 61 of the 163 (37%) patients who received ATD after ^{131}I treatment had recurrence of hyperthyroidism.

Discussion

We and others have compared standard versus calculated ^{131}I treatment for hyperthyroidism without finding any significant difference in regard to recurrence of hyperthyroidism between the two dosage schemes[15 17]. This is confirmed by the logistic regression analysis in the present study. In contrast to the univariate comparison the logistic regression model gives the independent associations with recurrence of hyperthyroidism, i.e. each of the significant associations are adjusted for the influence of the others. Thus the influence of ATD after ^{131}I treatment remains significant even when the influence of the other variables is also taken into account.

In 1954 Stanbury et al.[18] demonstrated that the administration of methimazole resulted in a decreased half-time for ^{131}I in the thyroid gland and a significant increase in the urinary excretion of iodide. Peters et al.[17] allowed ATD for 2-3 months after radioiodine application, but they do not mention the exact time interval from the ^{131}I treatment to the resumption of ATD, thus the possible influence of adjunctive ATD on outcome is difficult to assess. The high frequency of persistent hyperthyroidism among patients with Graves' disease from the calculated dose regime in our recent study was striking and might be explained by the administration of antithyroid medication to the patients after ^{131}I treatment[12]. Bertelsen et al.[19] aimed at ablating the thyroid gland with a standard 555 MBq ^{131}I dose for patients with Graves' disease but within one year hypothyroidism was induced in only 41%. Furthermore, 33% of the patients had to have additional ^{131}I therapy. ATD, which had been administered to nearly all of their patients until 7 days prior and again 4 days after ^{131}I treatment, may contribute to the high frequency of recurrence.

The thionamides inhibit the oxidation and organification of iodine and the coupling of iodotyrosyl residues to form iodothyronines[20]. As inhibitors of these peroxidatic reactions ATD may prevent organic iodination of ^{131}I.

Improved outcome of ^{131}I treatment of hyperthyroidism, i.e. less frequent recurrence of hyperthyroidism, can, according to our findings, be achieved simply by withholding ATD from patients treated with ^{131}I for hyperthyroidism. Thus a reduction of the impact of radiation on the environment may be achieved as well as a reduction in the financial expenses of repeated ^{131}I treatment of hyperthyroidism. Future regimes should also consider the administration of larger ^{131}I therapy doses or repeated doses, especially when treating large goiters.

Thyroid scintigraphy and a 24-hour ^{131}I uptake may, however, be reserved for diagnostic purpo-

Tab. II.
Logistic regression analysis for prediction of recurrence of hyperthyroidism after ^{131}I treatment.

		All variables included			Only significant variables included (Backward elimination procedure)		
Variable	Scoring	Regression coefficent	SE	p-value	Regression coefficent	SE	p-value
Gender	Females: 1 Males: 0	- 0.509	0.525	0.33			
Age	Years	- 0.00070	0.015	0.96			
Diffuse gland	Present: 1 Otherwise: 0	0.115	0.641	0.86			
Multinodular gland	Present: 1 Otherwise: 0	- 0.481	0.527	0.36			
^{131}I dose	MBq	- 0.0051	0.0019	0.008	- 0.0058	0.0018	0.001
Thyroid volume	$\log_{10}$(vol in ml)	3.158	1.107	0.005	3.013	1.038	0.004
24 h radioactive iodine uptake	%	0.023	0.015	0.13			
TSH	$\log_{10}$(units + 0.1)	- 0.206	0.369	0.58			
FT4I	$\log_{10}$(value)	0.743	1.284	0.56			
FT3I	$\log_{10}$(value)	1.512	1.342	0.26	2.408	0.886	0.007
ATD prior to ^{131} I treatment	Given: 1 Not given: 0	- 1.327	1.081	0.22			
PTU prior to ^{131}I treatment	Given: 1 Not given: 0	- 0.226	0.655	0.73			
NEOM prior to ^{131}I treatment	Given: 1 Not given: 0	- 0.328	1.508	0.83			
Duration of ATD	$\log_{10}$(month + 1)	- 0.162	0.463	0.73			
ATD after ^{131} I treatment	Given: 1 Not given: 0	2.368	0.901	0.009	1.781	0.516	0.0007
PTU after ^{131} I treatment	Given: 1 Not given: 0	0.026	0.681	0.97			
NEOM after ^{131} I treatment	Given: 1 Not given: 0	1.646	1.711	0.34			
Dose regime	Calculated: 1 Fixed: 0	0.103	0.343	0.76			
Constant		-7.740	3.118	0.014	-6.005	1.462	0.00006

ses, and are not to be recommended for the routine treatment of hyperthyroidism. We may still recommend a semiquantitative fixed dose regime taking thyroid size into account, a regime that allows the administration of ATD prior to ^{131}I treatment and does not take the type of thyroid gland into account [15].

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