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Differentiated thyroid cancer: comparison of therapeutic iodine 131 biological elimination after discontinuation of levothyroxine versus administration of recombinant human thyrotropin

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The biological elimination of therapeutic ^{131}I in patients with differentiated thyroid cancer (DTC), post total or near-total thyroidectomy, was compared after withholding levothyroxine suppression against administration of recombinant human thyrotropin without stopping levothyroxine. In 163 patients (group G_1) levothyroxine was withheld before ^{131}I therapy: in 138 patients the tumor was limited to the thyroid bed (group $G_{1.1}$) and in 25 patients metastases were present (group $G_{1.2}$). A second group of patients (G_2; n = 28) received ^{131}I therapy after administration of recombinant human thyrotropin without stopping levothyroxine. Mean retained ^{131}I activity (as a percentage of the administered dose) was 5%–29% (group $G_{1.1}$), 20%–43% (group $G_{1.2}$) and 1%–17% (group G_2). The effective half-life of ^{131}I was 0.59–0.69 days (group $G_{1.1}$), 0.87–1.22 days (group $G_{1.2}$) and 0.38–0.44 days (group G_2). In conclusion, the use of recombinant human thyrotropin to prepare patients with thyroid cancer for therapy with ^{131}I shortens its effective half-life and reduces its retained activity compared to preparation with discontinuation of levothyroxine suppression.

Key words: ^{131}I, thyroid cancer, retained activity, effective half-life

INTRODUCTION

THE THERAPEUTIC USE of iodine 131 (^{131}I) is a well-established procedure that supplements surgery in differentiated thyroid cancer (DTC). Although therapy with ^{131}I is beneficial to patients it can contribute to the radiation exposure of the population. The amount of retained ^{131}I activity in patients is critical for decisions relating to radiation protection: patients have to be hospitalized briefly until this activity is less than 555 MBq.[1–3] Retained activity depends on factors such as the uptake values, the presence of metastases, the consumption of fluids and the emptying of the bowel.[3] It is recommended that in addition to the physical decay of ^{131}I (half life 8.04 days), its biological elimination also be taken into account.

The use of recombinant human thyrotropin (rhTSH) in the management of DTC has increased steadily since the year 2000 when the European authorities approved its clinical use as an alternative means to raise the endogenous thyroid stimulating hormone (TSH) level prior to thyroglobulin (Tg) testing. Although rhTSH is currently used to prepare patients only for diagnostic purposes, it may be useful for preparing subsequent therapy with ^{131}I in some clinical circumstances.[4–6] In healthy volunteers the administration of rhTSH was uneventful.[7,8] Moreover, in patients with DTC it can bypass the weeks-long discontinuation of levothyroxine (L-T4) suppression and prevent the complications associated with the induced

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temporary hypothyroid state.[9–11]

The aim of this work was to assess, in patients with DTC treated with ^{131}I its retained activity and whole-body effective half-life and to investigate the impact of disease stage and rhTSH administration on these parameters.

SUBJECTS AND METHODS

Patients

The study included 191 patients with DTC and total or near-total thyroidectomy (39 men and 152 women; age range 16–75 years). The patients underwent ^{131}I treatment (68% initial ablative dose, 24% first subsequent dose and 8% second subsequent dose) at a major private hospital between September 2001 and July 2003. They required hospitalization of 1–3 days after receiving the therapeutic ^{131}I oral dose, until their external exposure rate was low enough to meet current discharge criteria.[12]

The patients were divided in two groups G_1 and G_2 (Table 1). In 163 patients (group G_1: 31 men and 132 women) L-T4 suppression was withheld for 40 days before ^{131}I therapy. Group G_2 patients (n = 28; 8 men and 20 women) did not stop L-T4 suppression and were euthyroid. They were given 0.9 mg rhTSH i.m. (Thyrogen, Genzyme Corp., Cambridge, Mass., USA) on 2 consecutive days followed by oral administration of ^{131}I.

According to the post-treatment whole body scan results the patients were further classified according to the TNM (Tumor–Node–Metastasis) system[13] as follows: group $G_{1.1}$ included patients whose disease was limited to the thyroid bed (n = 138; 24 men and 114 women) whereas group $G_{1.2}$ patients (n = 25; 7 men and 18 women) comprised cases that had distant metastases (i.e. $T_iN_jM_1$ where i = 1–4 and j = 0–1). In the patients of group G_2 the tumor was restricted to the thyroid bed similarly to $G_{1.1}$ patients (i.e. $T_iN_jM_0$ where i = 1–4 and j = 0–1).

All patients signed a written informed consent before treatment.

Pre-treatment uptake was assessed as follows:

Day 1: Uptake count for a ^{131}I (50 μCi) capsule with a thyroid uptake probe (Captus 600 Thyroid Uptake System, Capintec INC, Ramsey NJ, USA)
Administration of the capsule to the patient

After 24 h: Thyroid uptake count

After 48 h: Thyroid uptake count

Mean pre-treatment uptake and administered therapeutic doses for each group are also presented in Table 1. G_2 patients were administered higher therapeutic doses of ^{131}I compared to G_1 patients because their pretreatment uptake was lower.

Table 1 Patient groups according to tumor status and therapy used

Group	Therapy	Classification	No. of patients	Pretreatment uptake (%) (Mean ± SD)	Therapeutic dose (MBq) (Mean ± SD)
$G_{1.1}$	L-T4 discont.	$T_{1–4}N_0M_0$	115	2.7 ± 4.0	3537 ± 1066
		$T_{1–4}N_1M_0$	23	2.9 ± 4.3	3330 ± 884
$G_{1.2}$	L-T4 discont.	$T_{1–4}N_0M_1$	1	1.4	3237
		$T_{1–4}N_1M_1$	24	2.0 ± 2.8	4347 ± 1154
G_2	rhTSH	$T_{1–4}N_0M_0$	16	0.3 ± 0.7	4743 ± 1320
		$T_{1–4}N_1M_0$	12	0.4 ± 0.6	4588 ± 1114
	Total		191		

Table 2 Whole body ^{131}I effective half-life values (T_{eff-wb}) for each patient group

		T_{eff-wb} (days)		
		$G_{1.1}$	$G_{1.2}$	G_2
24 h	Mean ± SD	0.59 ± 0.25*	0.87 ± 0.33*	0.38 ± 0.10*
	Median	0.54	0.74	0.35
	Min–Max	0.28–1.80	0.61–1.41	0.25–0.57
48 h	Mean ± SD	0.60 ± 0.18#	1.03 ± 0.25#	0.41 ± 0.10#
	Median	0.56	1.01	0.44
	Min–Max	0.32–1.41	0.77–1.36	0.31–0.48
72 h	Mean ± SD	0.69 ± 0.21**	1.22 ± 0.3**	0.44**
	Median	0.64	1.31	NA
	Min–Max	0.41–1.29	0.89–1.46	NA

NA: not applicable (n = 1), *, #, **: $p < 0.001$; ANOVA

Table 3 Literature review of short-term ^{131}I therapeutic effective half-life values (mean and median) for cancer patients. All the findings were based on external exposure measurements

Patients/ Medical history	Effective half-life (days)			
	Type	Mean	Median	Reference
NA/NA	Thyroidal	7.3		1
	Extrathyroidal	0.32		
12 patients/total thyroidectomy	Whole body	0.51	0.48	15
238 patients/ total–near total thyroidectomy	Whole body	0.58	0.52	16
191 patients/ total–near total thyroidectomy	Whole body	0.59 ($G_{1.1}$)	0.54 ($G_{1.1}$)	Present study
		0.87 ($G_{1.2}$)	0.74 ($G_{1.2}$)	
		0.38 (G_2)	0.35 (G_2)	

NA: not available

Retained activity calculation

Patients were advised neither to drink any fluid nor urinate or defecate within two hours after ^{131}I administration (otherwise the patient was excluded from the study) for best radiopharmaceutical absorbance. After the 2 hour time period, the first measurement was taken assuming that at that time ^{131}I showed maximum dispersion through the patient's body. The retained activity calculation was based on external exposure rate measurements, as follows:

$$A_{wb\text{-}t} = E_{wb\text{-}t} * (A_{wb\text{-}2}/E_{wb\text{-}2}) \quad (1)$$

where $A_{wb\text{-}2}$ and $A_{wb\text{-}t}$ are the activities at 2 hours and t days post-administration respectively, while $E_{wb\text{-}2}$ and $E_{wb\text{-}t}$ are the maximum corresponding exposure rate values at a distance of one meter from patient's body at 2 hours and t days post-administration respectively.[3,14] Maximum exposure rates were measured with a calibrated ionization chamber (BICRON Surveyor 2000, Solon, Ohio) at 2, 24, 48 and 72 hours after administration (the last if the patient had not yet left the isolated therapy facility).

Whole body ^{131}I effective half life ($T_{eff\text{-}wb}$) calculation

The ^{131}I effective half-life in a patient's body was calculated according to the formula:

$$A_{wb\text{-}t} = A_{wb\text{-}0} * e^{-0.693t/T_{eff\text{-}wb}} \quad (2)$$

where $A_{wb\text{-}t}$ is retained activity t days post administration, as measured from equation (1) (in MBq), $A_{wb\text{-}0}$ is the administered activity (in MBq), t is the post-administration time (in days) and $T_{eff\text{-}wb}$ is the whole body ^{131}I effective half life (in days). In equation (2) $A_{wb\text{-}0}$ was assumed to be equal to $A_{wb\text{-}2}$ of equation (1), since the administered activity remained practically constant during the first 2 hours (actually 99% due to radioactive decay), in which the radiopharmaceutical was dispersed through the body.

Statistics

Comparisons of ^{131}I retained activity and of whole body effective half-lives at 24, 48 and 72 hours post-treatment among groups $G_{1.1}$, $G_{1.2}$ and G_2 were done with analysis of variance (ANOVA).

RESULTS

All patients tolerated the administration of ^{131}I well. Furthermore no untoward effects were noted in patients who received rhTSH.

With group $G_{1.1}$ patients being the reference group, group G_2 patients had significantly lower ($p < 0.001$) and group $G_{1.2}$ patients had significantly higher retained activity values ($p < 0.001$) at all times, respectively (Fig. 1): mean retained ^{131}I activity (as a percentage of the administered dose) was 5%–29% (group $G_{1.1}$), 20%–43% (group $G_{1.2}$) and 1%–17% (group G_2).

The effective half-life of ^{131}I (as estimated from equation (2) at 24 h, 48 h and 72 h), was significantly higher for group $G_{1.2}$, followed by that of group $G_{1.1}$ and was lowest for group G_2 ($p < 0.001$) (Table 2).

DISCUSSION

The excretion of ^{131}I in patients with DTC slows down as time passes after its administration. In Table 3 a literature review is attempted as far as ^{131}I effective half life is concerned. NRC effective half life calculation[1] was based on a bi-exponential mathematical model and the authors suggested that this model could be applied to all patients.

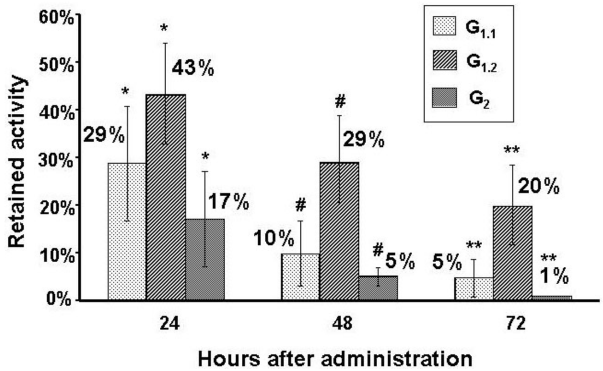

Fig. 1 Retained activity (percent of administered; mean ± SD) of ^{131}I in relation to time after administration. *, #, **: $p < 0.001$; ANOVA

Venencia et al.'s effective half life calculation[15] was based on accumulated dose measurements (for each patient), which were analyzed as a function of time. The authors concluded that effective half-life had a strong dependency on biological half-life and showed no relationship with administered activity. North et al.[16] used an operationally relevant method for estimating ^{131}I effective half-life and concluded that the NRC's value of 0.32 days for extrathyroidal iodine is far from being typical (being almost 50% less than their observed mean). The short-term (in the first 24 hours after ^{131}I administration) effective half-life values found in the present work are in accordance with those previously reported,[15,16] although measuring procedures are different (Table 3).

The findings of this work are in close agreement with those of North et al.[16] and Hennessey and Kreisman[17] who have shown that the retained therapeutic ^{131}I activity and effective half-life have far from "normal" values, in patients with total or near total thyroidectomy (Table 2 and Fig. 1, patients G_1). It is concluded that most ^{131}I is excreted within the first 48 hours, although this is more profound in $G_{1.1}$ patients. Figure 1 shows that retained activity after 48 hours was 10% for $G_{1.1}$ and 5% for G_2 patients, whereas for $G_{1.2}$ patients retained activity after 48 hours was 29%.

As far as the comparison between L-T4 replacement ($G_{1.1}$ patients) and rhTSH (G_2 patients) methods is concerned, Keizer et al.[18] studied 16 patients with metastatic or recurrent disease using dosimetric calculations that gave a highly variable tumor radiation dose with a median value of 26.3 Gy (range 1.3–368 Gy) when the patients were treated after rhTSH stimulation. They estimated a median ^{131}I effective half-life (from counts over each metastatic lesion visible on radiological images) of 2.7 days (range 0.5–6.5 days) based on the assumption of an exponential washout for ^{131}I. They compared their results with those of Maxon et al.[19] who had found effective half-lives of 3.3 ± 1.3 days for metastatic lesions of papillary DTC that responded to ^{131}I treatment and 1.9 ± 0.9 days for those that did not respond to treatment, performed in both cases after withholding L-T4 suppression therapy. The results of the present study showed lower effective half-life values (Tables 2 and 3, G_2 patients) that are more in accordance with those of Luster et al.[6] Comparison of relevant studies has shown that the whole body retention 48 h after rhTSH and ^{131}I administration is significantly lower than the corresponding retention value after withdrawal of thyroid hormone.[6] It has been suggested that this could be explained by the higher renal excretion of ^{131}I in euthyroid patients given rhTSH compared to those who are hypothyroid, an idea that Park et al.[20] also seem to share. In hypothyroid patients, renal function and renal clearance of ^{131}I are markedly decreased (50%) as compared to euthyroid patients receiving rhTSH.[20]

An additional parameter that influences the effective half-life of ^{131}I is probably the degree of patients' adherence to low-iodine diet instructions given by well before treatment. Goslings[21] in 1975 found an increase of approximately 20% in the biological half-life of ^{131}I in tumors due to a low-iodine diet, together with an increase of approximately 80% in tumor uptake of ^{131}I 24 h after administration.

Patients with DTC (and comparable extent of disease) ($G_{1.1}$ and G_2) given rhTSH with ^{131}I instead of discontinuing L-T4 therapy, show less retained activity and shorter effective half-life, even when being given higher doses of therapeutic ^{131}I. Patients with advanced disease ($G_{1.2}$) show more retained activity and longer effective half-life. The results of this investigation must be considered as preliminary, since more patients have to be studied (especially group G_2 patients). We emphasize however, that clinicians should scrutinize the selection of candidates for rhTSH, since its use may lead to important side effects (such as stimulation of tumor expansion with concomitant compression of key anatomical structures and neurological or other clinical complications) in patients with unknown skeletal or brain metastases.[7,22]

CONCLUSION

The use of recombinant human thyrotropin to prepare patients with thyroid cancer for therapy with ^{131}I shortens its radionuclide's effective half-life and reduces its retained activity compared to preparation with discontinuation of levothyroxine suppression. Among patients that received therapy with ^{131}I after discontinuation of levothyroxine suppression the retained activity was higher and the effective half-life of ^{131}I was longer in those that had metastatic disease compared to patients with tumors that were limited to the thyroid bed. Thus it appears that rhTSH is a less potent stimulator of ^{131}I uptake in thyroid remnant tissue.

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