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I–131 total body burden in postsurgical patients with thyroid cancer

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A whole body counter was used to study whole body retention of I–131 in order to estimate parameters of the retention curve, the total body absorbed dose, the correlation with the urine assay and the ratio of the ablation–therapeutic over the diagnostic body burden. The retention in 48 patients after surgery for thyroid cancer was measured 2, 24, 48 and 72 h after the diagnostic administration of 82±24 MBq, and in 26/48 patients 72 h after the therapeutic administration of 4361±216 MBq I–131. In 16 patients the activity of excreted urine was compared with in vivo measurements. In 44/48 patients the whole body retention curve was characterized by two exponential components, even in patients without evidence of radioiodine-concentrating thyroid tissue. The mean effective half–time was 10.9±2.1 h and the total body absorbed dose 5.0±2.2E-02 mGy/MBq. The urine assay overestimated whole body retention by a factor 2–5. The ratio of therapeutic versus diagnostic retention at 72 h was 0.82±0.41 and significantly negative correlated with the retention at 72 h and the residence time of diagnostic activity, and with the time period between surgery and diagnostic study. Radioiodine kinetics in postsurgical patients with thyroid cancer is dependent on different variables. Accurate in vivo measurements of whole body retention provided some novel data about non-standard kinetics of radioiodine, and timing and dosage during I–131 ablation procedure

Key words: thyroid neoplasms-surgery, body burden, whole–body counting, radioiodine kinetics, internal dosimetry; iodine radioisotopes, radioiodine therapy

Introduction

When a large amount of radioactivity is administered, the knowledge of the radiation burden on the critical organ and total body is certainly of importance not only for patients and hospital personnel, but also for the patient's family members and others. In the case of postsurgical patients with thyroid cancer, the ultimate goal to be achieved is a successful radioiodine ablation of residual thyroid tissue or functioning metastases using minimal amount of I–131 activity. Therefore, one may at the same time be concerned about the absorbed dose of more than

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80-300 Gy delivered to the metastatic thyroid cancer or thyroid remnant [1-5] and less than 2-3 Gy delivered to the blood,[1,2,6-9] the retained whole body activity of maximum 1110 MBq on the day of the patient's discharge from hospital,[10,11] the predictability of diagnostic study for subsequent therapy,[3,6,12,13] and the accuracy of methods for assessing patient body burden.[11,14]

The purpose of this work was to investigate the curves of initial whole body retention after the administration of the diagnostic activity of I–131 in patients following surgery for differentiated thyroid cancer, to estimate the mean whole body absorbed dose, to compare urine assay with whole body counting, and whole body retention after the diagnostic and ablation-therapeutic dose.

Patients and methods

A total of 48 patients were investigated after surgical thyroidectomy for thyroid cancer. Patients' demographic and clinical data are given in Table 1.

During a postsurgical waiting period of approximately 5-6 weeks, the patients were prepared by receiving no thyroxine supplements or iodine–containing medications. The assay of hormones was performed from the blood sample taken one day before diagnostic activity administration. Thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), thyroxine (T4) and thyroglobulin (Tg) concentrations were determined by means of Amerlite TSH-30, Ortho-Clinical Diagnostics Amersham (UK), Count-a-count Total T3 and T4, Diagnostic Products Corporation (USA) and HTGK-2, Sorin Biomedica Diagnostics (I) *in vitro* measurement kits respectively.

Whole body retention was measured using a shadow shield horizontal scanning bed whole–body counter (Canberra Accuscan Model 2260) equipped with a specially designed slit collimator for 10×10×40 cm NaI(Tl) detector.[15,16] Whole body counts were performed in 48/48 patients 2, 24, 48 and 72 hours after the administration of 82±24 MBq of diagnostic activity, and in 26/48 patients 72 hours after the administration of 4361±216 MBq I–131 of ablation activity. The initial measurement at 2 h, with no excretion meanwhile, served as the baseline standard for subsequent measurements. The geometric mean of net full energy spectrum counts obtained from supine and prone measurements was used to minimize the effects of activity distribution, body size and counting uncertainties. A correction for deadtime was made if it was necessary. The fitting of time–activity curve was performed for each patient using four point data set and method of non-linear regression.

Mean whole body absorbed dose D_{WB} was calculated according to the Medical Internal Dose Committee formalism [17] as

$$D_{WB} = \tilde{A}_{WB} S_{(total\ body \leftarrow total\ body)} \frac{m_{REF}}{m_{WB}}, \quad \tilde{A}_{WB} = \int_0^\infty A_{WB}(t)dt$$

where factor $\tilde{A}_{WB}$ represents whole body cumulated activity, $S_{(total\ body \leftarrow total\ body)}$ mean absorbed dose per unit cumulated activity (7.07E–7 and 8.89E-07 mGy/MBq for adult males and females respectively) and m_{REF}/m_{WB} ratio of the reference model to the patient specific whole body weight.

Whole body residence time (τ_{WB}) was calculated as

$$\tau_{WB} = \frac{\tilde{A}_{WB}}{A_0}$$

where A_0 is the administered diagnostic activity.

During the first three days after the administration of the diagnostic activity, the patients were advised to collect excreted urine. In 16 patients total one day urine volume was determined at 24, 48 and 72 h, and the activity of aliquot part was measured by Marinelli cup low level germanium gamma spectroscopy system (Canberra System 100).

Table 1. Demographic and clinical data of patient group

		Mean+SD	No. of patients
Age		46±12	48
Sex (M / F)			5 / 43
Weight (kg) / Height (cm)		71±12 / 164±8	48
Papillary / Follicular / Medullary			40 / 7 / 1
Surgery (tt / ntt)			35 /13
Time since surgery (days)		38±11	48
TSH (mIU/l)	nr:[0.2-4.2]	99.8±62.4 / ≥200	45 / 3
T3 (nmol/l)	nr:[1.4-2.8]	0.9±0.3	48
T4 [nmol/l]	nr:[65-155]	25.4±18.3 / ≤13	32 / 16
Tg (μg/l)	nr:[0-48]	21.8±15.4 / ≤5 / nd	18 / 21 / 9

SD-standard deviation; nd-not determined; tt-total thyroidectomy; ntt-near total thyroidectomy; nr-normal range;

The time-activity curve of the cumulative urine output was again fitted for each patient.

Gamma camera (Siemens Diacam) scans were performed two days after oral administration of the diagnostic activity and in 40 patient the ablation activity was administered orally 1-17 days later because of scintigraphically evident radioiodine-concentrating tissue in the thyroidal bed. Distant sites of activity accumulation were not found in any of the patients. Regarding scintigraphic images, the patients were classified into two groups: without (group A) and with (group B) evidence of residual radioiodine-accumulating tissue.

In 26 patients whole body retention of the ablation and the diagnostic activity on the third day (72 h) after activity administration was compared and expressed as a percentage ratio of relative observed (therapeutic) over predicted (diagnostic) value.

The results are expressed as a mean value±standard deviation (SD). Nonparametric statistical methods were applied in data analysis. The rank correlation coefficients and the comparison of two samples using Wilcoxon or Mann-Whitney U-test were used. The observed differences were considered significant at the level of $p<0.05$.

Results

Generally, the optimal fit was obtained using biexponential function $A_{WB}(t)=f_1A_0\exp(-B_1t) + f_2A_0\exp(-B_2t)$, where $A_{WB}(t)$ is the whole body activity at time t, f_1 is the fraction of initial activity A_0, and B_1 is the coefficient of effective clearance rate of component i (Figure 1.). Single exponential retention function was found only in 4/48 patients. The results of whole body retention analysis and dosimetric calculations are given in Table 2.

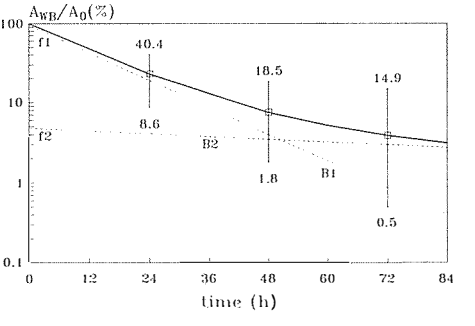

Figure 1. Illustration of biexponential whole body retention curve $A_{WB}(t)=f_1A_0\exp(-B_1t)+f_2A_0\exp(-B_2t)$ with high and low values of whole body activity A_{WB} over initial activity A_0 in postsurgical patients with thyroid cancer. Fraction f_1 of A_0 decays with effective removal coefficient B_1. Time-activity curve was fitted through mean values uncorrected for physical half-life.

Table 2. Parameters of whole body retention curve $A_{WB}(t)=f_1A_0\exp(-B_1t)+f_2A_0\exp(-B_2t)$ and dosimetric data of patients without (A) and with (B) evidence of radioiodine-concentrating tissue. fi is the fraction of initial activity A_0, B_1 coefficient of effective clearance rate of component i and D_{WB}, $T_{WB\ eff}$, T_{WB} are the whole body absorbed dose, effective half-time and residence time respectively

Parameter (× 10E-02)	A	B	A and B
f_1	78.7±22.1	85.4±17.7	84.5±18.1
B_1 (1/hr)	7.9±1.7	7.7±2.2	7.7±2.1
f_2	21.3±22.1	14.6±17.7	15.5±18.1
B_2 (1/hr)	3.3±1.0	2.7±1.4	2.8±1.3
D_{WB} (mGy/MBq)	4.7±1.2E-02	5.1±2.3E-02	5.0±2.2E-02
$T_{WB\ eff}$ (h)	10.6±2.1	10.9±2.2	10.9±2.1
τ_{WB} (h)	16.4±3.8	19.5±8.2	19.1±7.8

The effective half-times of excreted and retained activity (17.8±5.3 h vs. 11.0±2.6 h) were apparently different ($p<0.01$) but correlated ($r=0.47$, $p<0.01$). The sum of excreted and retained activity was generally about 90% of the administered activity, i.e. approximately 10% loss of activity was observed. Consequently, the whole body retention was overestimated by a factor 2-5 at the basis of urine assay.

The mean whole body retention at 72 h was 81.6±40.7% of that predicted by the diagnostic study. The therapeutic retention on the third day was significantly lower than diagnostic one (2.6±1.3% versus 4.5±4.1%, $p<0.01$), but they correlated well ($r=0.81$, $p<0.01$). The ratio of therapeutic to diagnostic whole body retention correlated significantly negative with diagnostic whole body retention at 72 h ($r=-0.83$, $p<0.01$), diagnostic whole body residence time ($r=-0.51$, $p<0.02$) and the time between surgery and diagnostic activity administration ($r=-0.47$, $p<0.02$), and weakly positive but not significant with TSH ($r=0.20$, $p<0.33$) and the time between diagnostic and therapeutic administration ($r=0.13$, $p<0.51$). Table 3. reveals the influence of different variables on the ratio of therapeutic and diagnostic whole body retention. Ideally the ratio should equal 100%.

Discussion

The coefficient of variation of the number of counts per unit of administered activity at 2 h (8%) was comparable with those (4-11%) obtained by measuring calibration sources in the thyroid, lung and gastrointestinal cavity of an anthropomorphic phantom.[15] *In vivo* measurements were so practically independent on patient's body size and activity distribution. The deadtime losses of any measurement were up to 10% and were taken into account. The statistical uncertainties of net counting rate were up to 1%.

Four measuring points are a minimal requirement for the employment of the fitting curve with four free parameters, while the established models of iodine kinetics justify the use of exponential function rather than any other function. Furthermore, patient's history and routine urine and blood analysis performed prior to activity administration indicated no abnormalities of renal function. The whole body retention curves were thus characterized by a first shorter, and a second longer lived component mostly being predominant from the second day. This is illustrated in Figure 1. and in Table 2. Only in 4 out of 48 cases no further improvement of fit was obtained by applying two instead of one exponential function (1/7 in group A and 3/41 in group B). The average effective half—

Table 3. Influence of different variables on the ratio of therapeutic ($A_{WB\ th}$) over diagnostic ($A_{WB\ dg}$) whole body activity at 72 h. A_0 is the initial activity, τ_{WB} is the whole body residence time, $T_{surgery\text{-}dg}$ the time between surgery and diagnostic study, and $T_{th\text{-}dg}$ between diagnostic and therapeutic administration

	$A_{WB\ th}/A_{WB\ dg}$ (%)	No. of patients	p
$A_{WB\ dg}/A_0$ (%)			
< 3	111.4±35.7	13	<0.01
> 3	51.8±15.7	13	
T_{WB} (h)			
< 16.5	98.9±42.4	13	<0.02
> 16.5	64.3±31.8	13	
$T_{surgery\text{-}dg}$ (d)			
≤ 38	100.7±47.1	13	<0.04
> 38	62.5±21.0	13	
TSH (mIU/l)			
< 50	64.1±41.0	8	<0.09
> 50	98.4±39.2	18	
Thyroidectomy			
total	90.5±41.7	17	<0.11
near total	64.9±35.0	9	
$T_{th\text{-}dg}$ (d)			
< 7	72.8±37.7	18	<0.12
≥ 7	101.4±42.7	8	

time of 10.9 h was, however, in very good agreement with the results of others,[7,11,18] but further analysis of component parameters revealed some interesting points. We found in group A the mean percentage intercept of the second component f_2 (>10%) significantly higher and the mean effective half–time $T_{2\ eff}$ (<48 h) shorter than the values reported by Edmonds et al. (<1% and >120 h).[18] The differences may be partly attributed to the measurements performed exclusively before, as in our case, or after the fourth day (Edmonds). A diagnostic workup study similar to our gave visually similar retention curves, although not much numerical data were provided.[9, 11] Since the retention during the postadministration three–day period could not be described by a monocompartmental model even in group A, the hypothesis of organic binding of radioiodine somewhere in the body appeared reasonable. The influence of activity retention in lesion or other normal tissue on the retention of whole body during distinct hypothyroid conditions seems to require more detailed investigation, as it has already been suggested.[5,19,20] Because of usually small amount of thyroid remnant and consequently low mean neck uptake of about 3%, the overlapping ranges of calculated parameters did not enable us to discriminate the patients of group A and B on that basis.

The latter also applies to the values of whole body radiation absorbed doses. They were calculated by assuming homogenous activity distribution and using recent 'S' values[17] corrected for the individual patient weight. The average value of 0.05 mGy/MBq was, however, not significantly different from the doses found by others.[7, 20]

The comparison of urine assay and whole body counting provided no particularly surprising information: retention overestimation of few times and 60% slower effective clearance rate of whole body activity as predicted by indirect in vitro measurement. Even with

the complete urine collection there will still be some other pathways (defecation, saliva, perspiration) of iodine excretion not taken into account. For example, a 10% loss in collection, resulting in change of cumulative excreted urine activity from 95% to 85%, will overestimate the retained body activity by factor three. For the reasons of accuracy and convenience, we also believe that carefully performed whole body counting is a superior method for assessing patient body burden[11,14]

A number of authors have found retained whole body activity or delivered dose to the target organ measured shortly after therapeutic administration significantly lower than the value predicted by diagnostic study,[3,6,12,13] but rarely with clear suggestion of the variables and degree of their influence. For the reasons of possible saturation, stunning or impairment of the radioiodine avid tissue caused by the diagnostic and therapeutic dose, the ratio of predicted over observed retention may not be a linear function of the ratio of administered diagnostic over therapeutic activity. The reduced therapeutic retention observed by us would cause about 15% shorter whole body effective half-time if monoexponential retention function was assumed. Table 3. virtually illustrates the whole body aspect of dramatically reduced neck uptake measured after the administration of the therapeutic activity in the similar patient group,[12] possibly mostly representing the effect of "stunned tissue". Approximately equal diagnostic and therapeutic whole body retention can be expected only if more detailed neck surgery is performed, which is likely to cause lower diagnostic retention, shorter residence time and higher TSH, if the period between surgery and diagnostic study is shorter, and that between diagnostic and therapeutic treatment longer. Regarding the time interval between surgery and diagnostic study, TSH levels were further analyzed owing to the suggested value of more than 30–50 mIU/l prior to the radioiodine treatment. The waiting period between surgery and diagnostic study of ≤4, ≤5, ≤6 and >6 weeks resulted in serum TSH values of 77.5±29.6 (n=6), 104.2±48.7 (n=14), 105.6±91.5 (n=13) and 99.6±53.6 mIU/l (n=12) respectively.

In conclusion, the diagnostic study using 37-74 MBq I-131 3-4 weeks after attempted total surgical thyroidectomy and radioiodine ablation-therapy more than 1 week later appears to be a reasonable step towards the optimization of timing and dosage during the ablation procedure. However, further investigation of radioiodine kinetics dependent upon different variables in postsurgical patients with thyroid cancer is necessary, and the whole body counting technique certainly has a role to play.

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