Influence of Dose Selection on Absorbed Dose Profiles in Radioiodine Treatment of Diffuse Toxic Goiters in Patients Receiving or Not Receiving Carbimazole

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We retrospectively reviewed the records of 224 patients with diffuse goiters treated with radioiodine, half of which received carbimazole. In all the cases, we carefully monitored the calculation of dosage. A lower percentage of early hypothyroidism but a higher failure rate was observed in the carbimazole subgroup. Nevertheless, after one year, a constant (4.5%) incremental rate of hypothyroidism was found regardless of carbimazole administration. Since we were able to precisely estimate the absorbed doses in our series, we evaluated by simulation the dosimetric profiles of nine methods of dose selection (MDS). These MDS were calibrated in such a way that the same threshold value of absorbed dose would always be reached at the thyroid level. We showed that the more elaborate the MDS, the more accurate the irradiation at the thyroid level and the lower the radiation dose administered. In patients not receiving carbimazole, a rapid MDS using modified early uptake measurements to predict the 24-hr actual value was found to be advisable. With patients receiving carbimazole and if a goal is to delay the occurrence of hypothyroidism, we advise MDS based on either a 48-hr uptake or on the calculation of the individual half-life.

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Despite almost 52 yr of experience with ^{131}I therapy for hyperthyroidism (*1*), little consensus exists among medical centers concerning a best method of dose selection (MDS). This probably results from the fact that ^{131}I's ability to render a patient euthyroid depends not only on the absorbed dose by the thyroid, but also on more or less unquantifiable elements such as radiosensitivity of the gland and thyroidal immunological status (*2,3*). Moreover, we agree that whatever the MDS used, long-term hypothyroidism is inevitable for patients with diffuse toxic goiters treated with ^{131}I. In this context, it is not surprising that many physicians have opted for simplified and inexpensive methods for determining radioiodine doses like the fixed dose or the weight modified methods.

These pessimistic considerations on thyroid dosimetry must be tempered. Indeed, most of the reports dealing with the clinical outcome of the ^{131}I therapy rely on very rough, if any, estimations of the absorbed dose. Two factors are involved here. First, the estimated size of the gland as determined by palpation is unreliable for dosimetric purposes since the average percent of error associated with clinical volume assessment is higher than 30% and may vary up to ±150% (*4*). However, an attempt to design more accurate methods of weight determination has been performed, first with planimetry (*5,6*) and more recently with ultrasonography (*7*). Second, the accuracy of irradiation is generally unknown but is thought to vary widely according to the method of dose selection applied. This latter point is of clinical importance since a lower incidence of early hypothyroidism was recently reported using calculated versus empirical methods of radioiodine dose selection (*8*).

For 40 yr, the custom in our department has been to perform a dosimetric study using a tracer dose in order to determine the therapy dose according to Marinelli's formula (*9*). This method, which unfortunately requires at least three visits for the patient, was chosen because some of us thought that a rather careful calculation of dosage would delay the occurrence of hypothyroidism and insure that the radiation dose administered was minimal.

Here, we report our results in a retrospective series of 224 irradiated patients, 107 receiving carbimazole, whose records had very complete dosimetric data. Since a reliable estimate of the cumulated uptakes was achievable in this series, we were able to compare the dosimetric pro-

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files, e.g., therapeutic and absorbed dose distributions, of nine methods of dose selection. Three of them are methods using early (3–6 hr) modified uptake measurements.

PATIENTS AND METHODS

The records of 224 patients treated with radioiodine during the period 1979–1989 were selected as follows. All the patients underwent a physical examination with special focus on signs of thyrotoxicosis and palpation of the gland. The thyroid biological status was always determined by radioimmunological assays: total T3 and T4 hormone levels and an index of free T4 (1979–1983); free T4 and T3 hormone levels and ultrasensitive TSH, since 1984 (Henning, Berlin, Germany) (*10*). Iodine-131 uptake measurements were performed after administration of a tracer dose at 3, 6, 24, 48 and 72 (or 96) hr, and at least twice after the 96th hr. Most of the medical records had a determination after the 240th hr (maximum 888 hr). These measurements were carried out as recommended by the I.A.E.A., using a collimated scintillation detector with a 44 × 51 mm Na(Tl) crystal and a Duphar Plexigas thyroid neck phantom (*11*). The extra-thyroidal neck activity was counted using a second identical probe viewing the knee and then subtracted from the neck counts. The same tracer dose (about 37 kBq per gram of estimated weight) allowed us to perform the rectilinear scan (MO5S, Mécasserto, Villejuif, France). The thyroid weight was derived from the surface of the gland using the planimetry's formula proposed by Himanka and Larsson (*5*). This surface was obtained from a 64 × 64 numerized image of the scan (Tridac BA 163/3, Intertechnique, France) after delimitation of ROI with the CINE 200 computer system (Intertechnique, France).

From at least 3 wk before until 2 wk after the therapy, 107 patients were treated with ^{131}I while receiving a constant dosage of carbimazole. Patients with iodine overload, as assessed by serum total iodine determination, and those with previous thyroid surgery or a history of ^{131}I administration were excluded. No differences were found between the whole population with diffuse toxic goiters treated in the same period and the selected ones in regard to age, sex and thyroid weight.

A follow-up review was undertaken in both subgroups. Mean follow-up periods were 61.6 mo and 65.2 mo for patients who were or were not treated with carbimazole, respectively. At this time, we were able to obtain follow-up information in about 80% of the patients. The percentage of patients who became hypothyroid was determined at 3 and 6 mo and then yearly up to 10 yr after the ^{131}I therapy. The hypothyroidism was always biologically assessed (*12*).

Absorbed Dose Determination (Gold Standard of the Study)

The absorbed dose by the thyroid was calculated according to the MIRD recommendations (*13*). We hypothesized that the volume irradiated was homogenous and isotropic. We postulated that the absorbed dose was 90% dependent on the β emission and considered that source and target were the same. We estimated the cumulated uptake assuming that the tracer dose and the therapy dose behave in the same manner (*14,15*). A direct calculation was done up to the 72–96 hr uptake measurement and thereafter by postulating a monoexponential decay of the isotope in the thyroid. We may thus state, if TD is the therapeutic dose to be administered, CUp the cumulated uptake and W the thyroid weight:

$$\text{absorbed dose (Gy)} = 0.0012 \times \text{TD (MBq)} \times \text{CUp (\%-hr)} \times [\text{W(g)}]^{-1}. \quad \text{Eq. 1}$$

Choice of Irradiation Levels

Since a major goal of this paper is to demonstrate that enormous scattering of the absorbed dose values will ensue according to the chosen MDS, we performed two series of calculations.

First, we calibrated the nine MDS in order that the mean value of the corresponding absorbed doses be about 60 Gy in both subgroups of patients. This value was not a goal in itself but corresponded to our clinical custom of using Marinelli's modelization and weight determination by planimetry.

Second, we calibrated the nine MDS in order that the 10th percentile value of the absorbed dose distribution be 60 Gy regardless of the methods tested in both subgroups. We hypothesized here that this threshold value was plausible to guarantee the cure in the majority of patients. A fixed dose of 370 MBq, which was reported to be effective for eliminating hyperthyroidism, led in our series of patients not receiving carbimazole to a 10th percentile value of absorbed dose slightly smaller than the 60 Gy (*16*). In any case, the same dosimetric evaluation could be performed choosing higher or lower threshold values.

Methods of Dose Selection—Therapeutic Doses

The design of the nine MDS and the corresponding equations of the therapeutic doses are reported in Table 1. Since the 24–48 hr uptake-based methods required two visits for the patients, we tested methods using a prediction of the (24–48 hr) uptake values from earlier (3–6 hr) actual measures. We plotted the early uptake measurements (x-axis) against the 24–48 hr uptake measurements (y-axis) and three "best fit curves" were generated. The predicted 24–48 hr uptake values were then derived from the equations of the fit curves presented in Table 2. The last studied MDS was the Marinelli method which postulates an immediate and maximal uptake, Up0, and a further monoexponential decay of the isotope in the thyroid: $\text{Up}(t) = \text{Up0}\ e^{-\lambda b t}$. The biological decay constant, λb, is derived from late uptake measurements performed from the second day until the third week after administration of a test dose, while the physical decay constant is set at ln 2/8.05. Having integrated (from $t = 0$ to $t = \infty$) the activity taken up by the thyroid, $A(t) = \text{TD Up}(t)e^{-\lambda e t}$, the cumulated activity becomes $\text{TD Up0}(\lambda e)^{-1}$ or, in terms of effective half-life (HL): $\text{TD Up0 HL}(\ln 2)^{-1}$. Using this specific value in Equation 1, and according to the specified units:

$$\text{TD(MBq, Marinelli)} = [\text{absorbed dose (Gy)} \times \text{W(g)}] \times [0.042 \times \text{HL (dy)} \times \text{Up0(\%)}]^{-1}.$$

Simulation

The numeric specific values involved in the design of the different MDS described above were determined by iterative computational calculations in both procedures: "mean and threshold 60 Gy" (Table 1). The absorbed doses are calculated according to Equation 1 with each patient serving as his or her own control. Note that the same thyroid weight estimation is used in all the calculations so that a possible error made on this assessment will weigh similarly regardless of the MDS tested.

TABLE 1
Design of Dose Selection Methods and Corresponding Equations of Therapeutic Doses (TD)

Methods of dose selection	Determination of the data required to calculate TD		
	TD equations	Specific data of the TD equations	
		No carbimazole	Carbimazole
Fixed dose*	TD = AD (0.0012 mean CUp/W)$^{-1}$	CUp/W (%-hr/g)	CUp/W (%-hr/g)
		210.9	162.3
Weight modified methods*		C(MBq/g)	C(MBq/g)
Actual weight	TD = CW	4.08 (6.78)	5.69 (20)
Three ranges of weight§	TD = 3 fixed doses according to W	TD(MBq) W(g)	TD(MBq) W(g)
if 0 ≤ W < 33 th	lower TD	195 (309) ≤50	245 (816) ≤48
if 33 th ≤ W < 66 th	medium TD	223 (330)	350 (843)
if W ≥ 66 th	upper TD	320 (515) >64	362 (998) >60
24-hr uptake based methods		C(MBq/g)	C(MBq/g)
Actual 24Up†	TD = (3.7CW)(24Up)$^{-1}$	2.03 (2.88)	2.03 (3.57)
Modified 3Up*	TD = (3.7CW)(p24Up)$^{-1}$	2.03 (3.33)	2.03 (5.31)
Modified 6Up*	TD = (3.7CW)(p24Up)$^{-1}$	2.03 (3.15)	2.03 (4.6)
48-hr uptake based methods		C(MBq/g)	C(MBq/g)
Actual 48Up†	TD = (3.7CW)(48Up)$^{-1}$	2.03 (2.73)	2.03 (3.08)
Modified 6Up*	TD = (3.7CW)(p48Up)$^{-1}$	2.03 (2.92)	2.03 (4.4)
Marinelli method††	TD = (ADW)(0.042 HLUp0)$^{-1}$	individual HL and Up0 determination	

The data in bold characters presented in the equations of the therapeutic doses are specified in the right columns of the table, according to the both procedures of simulation: "mean 60 Gy" and "threshold 60 Gy" (in brackets). The ranges of thyroid weights are defined by the percentiles (th) of their distribution (§). Patient's visits: one day (*), two days (†), four or more days (††).

AD = absorbed dose (Gy, specific values are given in Tables 4 and 5), CUp/W = cumulated uptake per gram (%-hr/g), W = thyroid weight (g), C = concentration (MBq/g), XUp = uptake measurement (%) performed at X hour, pXUp = predicted X uptake from earlier actual measurements (specific values are given in Table 2), HL = half-life and Up0 = uptake at time 0.

Statistics

Patients' characteristics and real dosimetric data were compared using a factorial analysis of variance according to carbimazole administration. Within each subgroup, the comparisons between either the therapeutic doses or the absorbed doses obtained with the two procedures of simulation used a "within methods" one-factor analysis of variance (repeated measures). Values obtained with the different MDS are also compared to the data of the fixed dose method in both procedures using a many-one multiple comparison t-test according to the method of Dunnett (*17*). The rate of hypothyroidism was calculated for the 1–10 yr period of follow-up using the lifetable technique. The statistical method used was the logrank test (*18*).

RESULTS

The unmodified 3–6 hr uptake measurements underestimated the 24- and 48-hr values (Table 2). Conversely, the 24- and 48-hr estimates calculated from the 3- and 6-hr measurements using the best fit equations, were similar to the actual values ($p = 0.78$ to 0.99). Note that the "best fits" were exponential in patients not receiving carbimazole and were otherwise linear. As a general rule, predicted and measured 24–48 hr uptake values correlated more closely in the carbimazole subgroup.

Patients' characteristics and real dosimetric data are shown in Table 3. Higher therapeutic doses were administered to patients on carbimazole using Marinelli's method which aims at 60 Gy. This paralleled the lower values of cumulated uptake, effective half-lives and zero uptake found in this subgroup. Most of the patients received less than 30 mg a day. A higher level of second doses was administered in the carbimazole subgroup, generally because a persistence of hyperthyroidism was observed when an attempt was made to stop the administration of the carbimazole during the first few months following the ^{131}I therapy. A significantly lower percentage of early (1 yr) hypothyroidism was seen in patients receiving carbimazole, but the average incidence rates for hypothyroidism (during the 1–10 yr of follow-up period) were comparable regardless of carbimazole administration.

The predicted therapeutic doses (MBq) and the corresponding absorbed doses (Gy) calculated for the different MDS according to the first procedure of simulation ("mean 60 Gy") are reported in Table 4.

No difference was found between the values of therapeutic doses actually administered and simulated using the Marinelli modelization. Absorbed doses were found to be underevaluated by about 11% with this method, which theoretically aimed at 60 Gy. In any case, the more elaborate the MDS (Marinelli, single uptake-based, uptake-free methods in descending order), the more accurate the thyroid irradiation was. A similar mean level of therapeutic doses grossly corresponded to a similar mean level of absorbed dose except for the fixed dose which

TABLE 2
Uptake Values Measured at 3, 6, 24 and 48 Hours

Predicted ^{131}I uptake	Best fit equations	
	No carbimazole	Carbimazole
24Up from the 3Up	32 log 3Up + 14	0.87 3Up + 18
24Up from the 6Up	64.6 log 6Up − 46	0.89 6Up + 11
48Up from the 6Up	49.4 log 6Up − 24	0.82 6Up + 11
^{131}I uptake values	No carbimazole	Carbimazole
Measured 3Up	52 ± 21	36 ± 19
Measured 6Up	62 ± 18	44 ± 20
Measured 24Up	68 ± 12	50 ± 20
Predicted 24Up		
From the 3Up	68 ± 07 (0.61/0.12)*	50 ± 17 (0.84/0.06)*
From the 6Up	68 ± 10 (0.77/0.07)*	50 ± 18 (0.92/0.04)*
Measured 48Up	64 ± 12	47 ± 19
Predicted 48Up		
From the 6Up	64 ± 07 (0.6/0.12)*	47 ± 17 (0.85/0.06)*

*Correlation coefficients (r, $p < 0.0001$) between the measured uptake values and the corresponding predicted values from earlier measurements are given in the brackets: (r/SE), where SE is the standard error on the slope.

The 24-48 hr uptake values can be predicted from the earlier (3, 6-hr) actual measurements using the "best fit equations".

Uptake values (%) are mean ± s.d.

Log = decimal logarithm and XUp (%) = uptake value at time X (hr).

was found to deliver slightly lower therapeutic doses. Finally, the results of the uptake-free MDS appeared to be imprecise in the carbimazole subgroup (CV of absorbed dose: 50%–68%).

Once calibrated, the different MDS were no longer comparable according to the second procedure of the simulation ("threshold 60 Gy"). It is clear that using the more elaborate MDS, lower mean therapeutic doses and lower mean absorbed doses could be delivered at the same time (Table 5). Here again this was especially evident in the carbimazole subgroup where a clear-cut discrepancy was observed between uptake-free and uptake-based MDS in regard to the decrease of administered radiation.

Lastly, we found no linear correlation between the thyroid weights and the levels of irradiation obtained with Marinelli's method. This was also the case with all the single uptake-based methods in the carbimazole subgroup (a very weak positive correlation was found in patients not receiving carbimazole). On the other hand, the fixed dose method strongly overirradiated the smaller glands regardless of carbimazole administration.

DISCUSSION

Iodine-131 is a simple, effective and apparently safe treatment for patients with diffuse toxic goiters (*19,20*). In western Europe, its indications have slowly been extended to include younger patients (*21,22*). However, many clinicians still reserve this therapy for men and women over 40. The rationale for this restriction is the possible risk of genetic abnormality in the offspring of treated women and a possible elevated cancer risk after ^{131}I exposure. An excess mortality rate due to cancer of the stomach was recently reported in the follow-up of patients treated with ^{131}I for thyrotoxicosis (*23*). Thus, we believe that methods of dose selection should conciliate three major goals: patient convenience, clinical success and minimum radiation administered.

Our clinical results, based on a calculated therapeutic dose according to Marinelli, are in agreement with the last two goals. In patients who received ^{131}I as the sole treatment, we administered rather low therapeutic doses and retreatment was required in less than 15% of the cases. In addition, a non-negligible percentage of the patients remained euthyroid during the first few years after the ^{131}I therapy. However, at 10 yr, a great majority of these patients became hypothyroid, while about 40% of the patients co-treated with carbimazole were found to be still euthyroid. In this latter subgroup, this paralleled the lower occurrence of hypothyroidism which only reflected the lower rate of early hypothyroidism. The incidence of late myxoedema was comparable regardless of carbimazole administration. Similar findings were previously reported when rather comparable modalities of ad-

TABLE 3
Dosimetric Data and Clinical Outcome of Two Groups of Patients Receiving or not Receiving Carbimazole

Parameters	Patient group		p
	No carbimazole	Carbimazole	
n	117	107	
Age (year)	59 ± 13	58 ± 12	ns
Thyroid weight (g)	62 ± 22	58 ± 23	ns
Uptake at time 0 (%)	66 ± 14	50 ± 20	0.0001
Effective half-life (day)	5.97 ± 1.00	5.41 ± 1.31	0.0002
Cumulated uptake (%-hr)			
Study reference	12247 ± 3587	8784 ± 4176	0.0001
Marinelli method	13760 ± 3525	9679 ± 4737	0.0001
Therapeutic dose (MBq)*	257 ± 116	420 ± 336	0.0001
Carbimazole (mg)	—	22 ± 12	
Second dose (%)	12.8	21	0.0001
Hypothyroidism†			
Incidence at one year (%)	34.9	15.1	0.001
Average incidence rate (% per year)	4.54	4.50	ns

Values are mean ± s.d. Cumulated uptakes are presented for the reference method of the study and Marinelli modelisation. Two-by-two comparisons were made using a factorial analysis of variance, according to carbimazole administration. The therapeutic dose which was actually administered was determined using the Marinelli method (*). The percentages of hypothyroidism at 1 yr were compared using the chi-square test while the incremental rates of hypothyroidism, corresponding to the 1–10 yr of follow-up, were compared using the log rank test (ns = $p > 0.05$).

TABLE 4
Predicted Therapeutic Doses (MBq) and Corresponding Absorbed Doses (Gy) According to the First Simulation Procedure, "Mean 60 Gy" (See Choice of Irradiation Levels)

	Patient group			
	No carbimazole (n = 117)		Carbimazole (n = 107)	
Methods of dose selection	MBq	Gy	MBq	Gy
Fixed dose	237	60 ± 22	308	60 ± 33
Weight modified methods				
Actual weight	254* ± 89	60 ± 18	324 ± 133	60 ± 32
Three ranges of weight	246 ± 54	60 ± 18	319 ± 353	60 ± 29
24-hr uptake based methods				
Measured 24Up	259† ± 99	60 ± 15	383* ± 318	57 ± 17
Modified 3Up	255* ± 95	61 ± 19	336 ± 140	58 ± 25
Modified 6Up	256* ± 95	60 ± 18	345 ± 164	57 ± 23
48-hr uptake based methods				
Measured 48Up	279† ± 111	64* ± 14	424† ± 384	60 ± 16
Modified 6Up	272† ± 98	64* ± 19	364 ± 168	61 ± 24
Marinelli method	240 ± 119	53† ± 09	418† ± 428	54* ± 07
p (ANOVA within methods)	0.0001	0.0001	0.0001	0.0508

Values of the therapeutic and absorbed doses are mean ± s.d. All the methods of dose selection are calibrated in order to reach a same mean level of irradiation set at about 60 Gy. The methods based on modified early uptake measurements are presented in Tables 1 and 2. Statistics: one factor analysis of variance within the different methods of dose selection. Comparisons between the data obtained with the different methods of dose selection and the fixed dose method are performed using the many-one t-test of Dunnett (*$p < 0.05$, †$p < 0.01$).
XUp = uptake measurement at X hour.

ministration of the antithyroid drugs were applied (*24,25*). When antithyroid drugs are given only pre- or post-treatment, no reliable assessment of the absorbed dose can be achieved because uptake and kinetics of the tracer dose will no longer reflect the therapy dose. Thus, it is not surprising that in such conditions contradictory clinical data have been reported concerning the role of this drug as an adjuvant of the ^{131}I therapy (*26–28*). A second

TABLE 5
Predicted Therapeutic Doses (MBq) and Corresponding Absorbed Doses (Gy) According to the Second Simulation Procedure, "Threshold 60 Gy" (See Choice of Irradiation Levels)

	Patient group			
	No carbimazole (n = 117)		Carbimazole (n = 107)	
Methods of dose selection	MBq	Gy	MBq	Gy
Fixed d ose	408	103 (150)	850	166 (306)
Weight modified methods				
Actual weight	423 ± 148	100 (142)	1144* ± 468	211* (369)
Three ranges of weight	385 ± 93	93* (129)	886 ± 80	170 (294)
24-hr uptake based methods				
Measured 24Up	371* ± 142	86* (117)	674* ± 559	100* (137)
Modified 3Up	418 ± 156	99 (140)	879 ± 367	150 (230)
Modified 6Up	398 ± 147	93* (134)	783 ± 372	130* (193)
48-hr uptake based methods				
Measured 48Up	377* ± 150	86* (112)	644* ± 584	91* (119)
Modified 6Up	393 ± 141	93* (130)	789 ± 364	131* (198)
Marinelli method	334* ± 165	74* (88)	556* ± 569	71* (81)
p (ANOVA within methods)	0.0001	0.0001	0.0001	0.0001

Values of the therapeutic doses are mean ± s.d. Absorbed dose values are: mean (90th percentile value of the dispersion). All the methods of dose selection are calibrated in order that the 10th percentile value of the absorbed dose dispersion be exactly 60 Gy. The methods based on modified early uptake measurements are presented in Tables 1 and 2. Statistics: one factor analysis of variance within the different methods of dose selection. Comparisons between the data obtained with the different methods of dose selection and the fixed dose method are performed using the many-one t-test of Dunnett (*$p < 0.01$).
XUp = uptake measurement at X hour.

advantage of the combination therapy is that the patients are rendered clinically euthyroid shortly after the antithyroid drug administration. Afterwards, radioiodine therapy may be proposed in comfortable and safe conditions for the patient. The major problem with combined therapy is that higher therapeutic doses are to be administered. Therefore, the choice of the MDS appeared to be crucial and we found that the uptake-free MDS were far from being advisable in such a case. The mean value of 420 MBq, which was administered in our group of patients co-treated with carbimazole, was found acceptable considering that the reported range for therapy using a fixed dose varied between 370 MBq (87% of cure at 1 yr) to 555 MBq ("ablative dose"), even in patients not receiving carbimazole (*16,29*).

The well-known bimodal pattern of onset of hypothyroidism (*30–32*) was also found in our group of patients. From a theoretical point of view, it was interesting to note that even though a comparable mean level of absorbed dose was delivered in both subgroups, there was a lower incidence of early hypothyroidism in patients receiving carbimazole. Antithyroid agents exert their action mainly by inhibiting TPO-catalyzed iodination (*33*). However, this inhibition is very heterogenous among the follicles. In addition, beta emitters are effective only on a short path length since for an ^{131}I beta point source in water, 90% of the point source energy will be absorbed at a distance of about 800 μm (*34*). In a recent paper dealing with beta dosimetry of ^{131}I-labeled antibodies in follicular lymphoma, which are known to have a nonhomogeneous pattern of uptake, the localized dose was reported to vary by a factor of two from the average tissue dose (*35*). Thus, we suggest that the radioprotective effect observed in the carbimazole subgroup should correspond to a rise of the heterogeneity of the beta radiation dose distribution. Finally, it is easy to imagine that a persistence of hyperthyroidism is expected if too many functional follicles are blocked and therefore can no longer assure a significant level of ^{131}I iodinations. On the other hand, the gamma radiation dose delivered to the thyroid is not sensitive to millimetric scaled modifications of the dose distribution and can damage follicles regardless of their functional status. This should partly account for the same incremental rates of late myxoedema observed, regardless of carbimazole administration and explain why long-term hypothyroidism is inevitable.

The attempt to design optimum calculation of dosage justifies itself only if a rather accurate weight determination is possible. In simple Graves' disease, the weight is directly proportional to the functioning mass (*2*) and only moderate variations in the shape of the thyroid are observed. Planimetry, which was introduced 40 yr ago, was reported to perform a more reproducible and accurate assessment of thyroid volume than palpation, with average errors of 6%–20% when compared to anatomical findings (*5,6,36*). In any case, we believe that the use of ultrasonography, which has a 5%–15% coefficient of variation in determining the thyroid volume (*4,7*), would justify a renewal of interest in thyroid clinical dosimetry.

According to this simulation, the single-uptake based methods and the Marinelli method had similar dosimetric profiles in patients not receiving carbimazole. As the former require only two examinations for the patients, they would appear to be much more advisable. In patients receiving carbimazole, the main benefit observed with the Marinelli method was a strong decrease in the proportion of patients who would be needlessly overirradiated at the thyroid level. Since in our department we hope to clinically delay the occurrence of hypothyroidism for as long as possible, we still calculated the isotope's half-life in this case using only two or three late uptake measurements. Nevertheless, if a prerequisite is to achieve treatment within two visits, the method using a single uptake measurement at 48 hr was found to be better in regard to radiation being administered.

Since same day assessment of thyroid hormone levels and ultrasensitive TSH is now routinely available, fast methods of dose selection are widely used. The fixed dose method is obviously simple and cost-effective for both the patient and the hospital. Unfortunately, the values of the fixed therapeutic dose are empirically derived from the results of the patients who have the most unfavorable dosimetric parameters such as an unsuspected low ^{131}I uptake or a large thyroid weight. This is why a considerable rise in the levels of irradiation was found using the fixed dose, especially in patients receiving carbimazole which clearly blunts uptake and half-life values. The use of a simple weight modulation in calculating the therapeutic dose could appear to be suitable for patients not receiving carbimazole. Indeed, the method based on three ranges of thyroid weight led to rather similar levels of irradiation in comparison to the values found with the 24-hr uptake based method. However, the choice of the thresholds of weight remains necessarily arbitrary. In addition, a little variation in estimating the thyroid weight will result in a large variation of the therapeutic dose to be administered, especially in patients whose actual thyroid weights are close to these thresholds.

New rapid methods were devised using predicted uptake measurements from earlier (3–6 hr) actual measures. This practice was recently suggested to achieve reliable treatment of diffuse goiters (*16*). The measure of early uptake values must always take into account the extrathyroidal activity which is not negligible in the first few hours following the administration of the test dose. The absorbed doses corresponding to these methods based on predicted uptake measurements were closely correlated to those based on actual measures ($r = 0.79–0.93$, s.e. on the slope <0.05). The highest value of correlation was observed in patients not receiving carbimazole when the 6-hr uptake measurement was used to predict the 24-hr value. In patients receiving carbimazole, these methods

would be less useful because they led to therapeutic dose levels which are comparable to the fixed dose.

As opposing goals are to be met at the same time, no method of dose selection can achieve the miracle cure. The more elaborate methods are time consuming but are more advisable in regard to radioprotection and, to a lesser extent, the clinical outcome. The choice of a rapid method using a measured 6-hr uptake to predict the 24-hr value could offer a good compromise for patients not receiving carbimazole. When ^{131}I therapy is performed in patients receiving carbimazole, we advise either choosing the method based on the actual 48-hr uptake measurement or determining the individual effective half-life, since we have shown that this latter method delays the occurrence of hypothyroidism while keeping radiation exposure at a reasonable level.

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