KINETICS OF LARGE THERAPY DOSES OF ^{131}I IN PATIENTS WITH THYROID CANCER

B. Singh, S. M. Sharma, M. C. Patel, K. V. Raghavendran, and M. Berman*

Tata Memorial Hospital, Patel, Bombay, India

Radioiodine kinetics were studied in 16 patients treated with a postsurgery ablation dose of radioiodine ranging from 90 to 450 mCi. The data obtained from serial whole-body radioactivity measurements, thyroid uptakes, plasma radioactivity, and protein-bound iodine radioactivity measurements in the patients could be fitted to the Brownell model which was modified to simulate an unsteady state by varying the turnover rates between thyroid and plasma compartments (L_{21} and L_{12}). Although there appears to be a linear relationship between the radiation dose delivered to the thyroid and the maximal radioiodine concentration, there is a change in the slope beyond ^{131}I concentration of 0.4 mCi/gm of thyroid tissue. More data with higher radioiodine doses are necessary to confirm a saturation effect.

Iodine kinetics with tracer doses of radioiodine have been studied by many workers and commonly a three-compartment model has been proposed to interpret the kinetic data (*1–3*). A more universal and detailed model has been proposed by Berman, et al (*4*). The iodide system is in a steady state with tracer doses of radioactive sodium iodide and the compartment sizes remain constant. However, with large therapy doses of ^{131}I the thyroid compartment size and the turnover rates may not remain constant during the period of observation due to acute radiation damage to the thyroid. This paper proposes a model to describe radiation damage to the thyroid from radioiodine therapy doses and the resulting effects on iodine kinetics. The model is consistent with the experimental data observed after the administration of radioiodine to patients with thyroid cancer. The radiation dosage to thyroid, total body, blood, and metastases resulting from such kinetics are also computed.

MATERIALS AND METHODS

Sixteen patients suffering from differentiated carcinoma of the thyroid were studied. A therapeutic dose of ^{131}I as sodium iodide was administered orally to ablate residual thyroid tissue or functioning thyroid malignancy or both. The dose of radioiodine varied from 90–450 mCi depending upon the uptake of ^{131}I and the mass of the iodide-concentrating tissue to be ablated. Five of the 16 patients were treated with an ablation dose more than the conventional maximum dose of 250 mCi. A larger dose was given to these patients since the area to be ablated had poor ^{131}I retention. The following observations were made after the administration of radioiodine.

Whole-body radioactivity measurement. Serial whole-body radioactivity measurements were performed at ½ hr, 2 hr, 4 hr, 8 hr postadministration and then at 24 hr intervals up to 6–13 days. The radioactivity in the whole body was expressed as a percentage of the dose administered. The patient served as his own standard. The maximum whole-body count was taken as 100% of the dose administered.

The whole-body counter consisted of a 3 × 3-in. NaI(Tl) activated crystal detector coupled to a spectrometer and a scaler. A focusing collimator (19 holes, 4.5 cm focal distance) was used to cut down the sensitivity and the background counts. The patient was kept in a standing position at a distance of 13 ft. In the area occupied by the patient, the point-source response variations at different posi-

Received Feb. 27, 1973; revision accepted Mar. 6, 1974.

For reprints contact: Balvinder Singh, Bhabha Atomic Research Center, Medical Division, Modular Laboratories, Trombay, Bombay-85, India.

* Present address: Mathematical Biology Section, Laboratory of Theoretical Biology DCBD, National Cancer Institute, NIH, Bethesda, Md.

tions were less than 10% of the maximum counting rate observed. The counting system gave 280 counts/min/mCi for ^{131}I with a background of 400–500 cpm.

Thyroid uptake measurements. The radioiodine uptake by the thyroid was computed by subtracting the whole-body counts obtained with the thyroid region covered by a standard lead shield from the total whole-body counts. The radioactivity in the thyroid at any time was expressed as a percentage of dose administered. Similar measurements were carried out for determining the uptake of ^{131}I by the functioning metastasis.

Plasma radioactivity measurement. After radioiodine therapy serial blood samples were collected in a heparinized vial at 2, 4, and 8 hr on the first day and then at 24 hr intervals for 5–13 days. Plasma radioactivity was measured in a well-type scintillation counter. Blood volume was assumed to be 7% of the body weight and plasma volume was derived from the hematocrit value. Total radioactivity in the entire plasma volume was expressed as a percentage of the administered dose. In order to express the plasma activity as a percentage of the administered dose, the response of the well counter used for the study was calibrated against the response of the whole-body counter.

Protein-bound iodine radioactivity measurements. Plasma proteins were precipitated with 20% trichloroacetic acid (TCA) and then washed three times with 20% TCA. The washed precipitate was dissolved in 20% NaOH and counted in the well-type scintillation counter. The radioactivity was expressed as percentage of dose administered.

Estimation of thyroid weight. The mass of the thyroid was estimated from the scintiscan taken 48 hr after administration of a tracer dose of ^{131}I. The weight of the thyroid was derived from the following formula assuming the thickness of thyroid lobe to be equal to two-thirds of the width.

Weight of lobe in gm =

$$\frac{\text{length (cm)} \times \text{width (cm)} \times \tfrac{2}{3} \text{ width (cm)}}{2}$$

Weights of the two lobes were added to obtain total thyroid weight in patients where both lobes were visualized.

Estimation of the weight of metastasis. Metastases in the lymph nodes were taken to be spherical and their weight was derived from the volume of sphere. Weight of a bone metastasis was determined from its dimensions seen in the scan.

Kinetic modeling. The model described by Brownell, et al (*1*) was modified to simulate the unsteady state by varying the turnover rates. Simulation of the model was carried out on UNIVAC-1108 computer

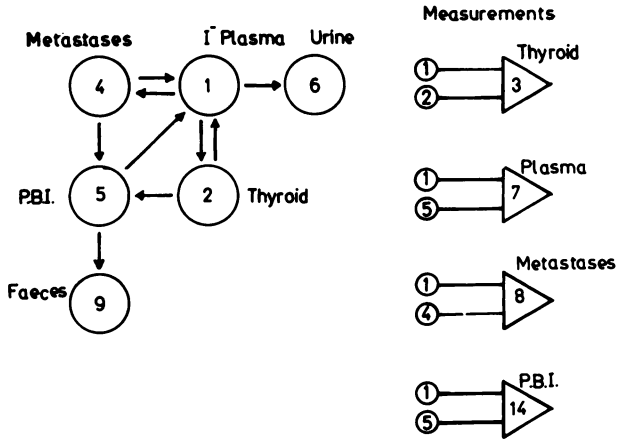

FIG. 1. Iodine kinetics model. Numbered circle represents compartment (physiological or biochemical subdivision of the system) such that the specific activity within the compartment is constant at any particular moment. Flow of radioactivity between the compartments is governed by Eq. 1 (see text). Triangles shown on right are measurements, experimentally observed value of radioactivity at site mentioned, having contributions from different compartments (Eq. 2, see text). Small circle joined to triangle represents corresponding compartment shown in left part of figure.

using the SAAM computer program described by Berman, et al (*5*).

The model illustrated in Fig. 1 is defined by the following equations:

$$\frac{dF_i}{dt} = \sum_j L_{ij}F_j - \sum_j L_{ji}F_i \qquad (1)$$

$$Q_i = \sum_j S_{ij}F_j \qquad (2)$$

where F_i is the radioactivity at time t in the compartment i (represented by circle i, Fig. 1).

L_{ij} is the fractional turnover rate, defined as the fraction of compartment j entering compartment i per unit time (represented by arrow from compartment j to compartment i, Fig. 1).

Q_i is the radioactivity measured in the set of measurement i (e.g., for i = 7, Q_7, represents the measured radioactivity in plasma, which is partly due to the radioactivity from inorganic iodide F_1 and partly due to radioactivity from protein-bound iodine, F_5). Q_i is represented by triangle i in Fig. 1.

S_{ij} is the fraction of compartment j seen in the set of measurement i (represented by line joining circle j and triangle i, Fig. 1).

The subscripts i and j have only the values that are shown in Fig. 1 as the numbered circles and triangles. The S_{ij} and L_{ij} not shown in Fig. 1 are zero.

The following hypotheses were introduced as we could not fit the data to a model with the time-independent constant turnover rates (L_{12} and L_{21}).

1. Radiation within the thyroid destroys the tissue (T) at a rate proportional (C_1) to the radioactivity within the thyroid (A_{th}).

$$\frac{dT}{dt} = -C_1 T_{th}(t) \qquad (3)$$

or

$$T(t) = T(0) - C_1 \int_0^t A_{th}(\theta)\, d\theta \qquad (4)$$

2. The rate of uptake of iodide by the thyroid is proportional to the amount of active tissue remaining.

$$L'_{21} = L_{21} \frac{T(t)}{T(0)} \qquad (5)$$

Where L_{21} is the value of this parameter at $t = 0$ and L'_{21} is the value at any time "t".

3. When the tissue is destroyed, a proportional amount of iodine is released as iodide.

$$L'_{12} = L_{12} + \frac{1}{T(t)} \cdot \frac{dT}{dt} \qquad (6)$$

Since it was not apparent at the outset that functioning metastases would have an iodine kinetic pattern similar to that of thyroid, no attempt was made to formulate any hypothesis linking the effect of metastases irradiation and the associated fractional turnover rates. Moreover, no figures on the fractional turnover rates essential for the formulation and confirmation of the hypothesis have been reported in the literature.

Computation of radiation-absorbed dose to various body organs. Computation of absorbed dose was done according to the method outlined by Loevinger and Berman (*6*). The equilibrium dose constants were taken from Dillman (*7*). The absorbed fractions were taken as published by Brownell, et al (*8*). Millicurie day required for computation of absorbed dose was calculated from the model simulations (F_i). The model was simulated with values for L_{ij} and S_{ij} equal to the values for normals as published in literature (*1–4*). Variations in L_{12}/L_{21} and radiation-absorbed dose to various body organs were determined for a tracer dose of 1 μCi of ^{131}I in a standard man.

RESULTS

Figure 2 shows the pattern of total-body uptake, thyroid uptake, and plasma and protein-bound ^{131}I activity in a patient studied over a period of 12 days after the administration of a therapeutic dose of ^{131}I. The points are experimental observations whereas the lines drawn are values predicted by the model. Figure 3 shows the A_{th} (the millicurie days in thyroid),

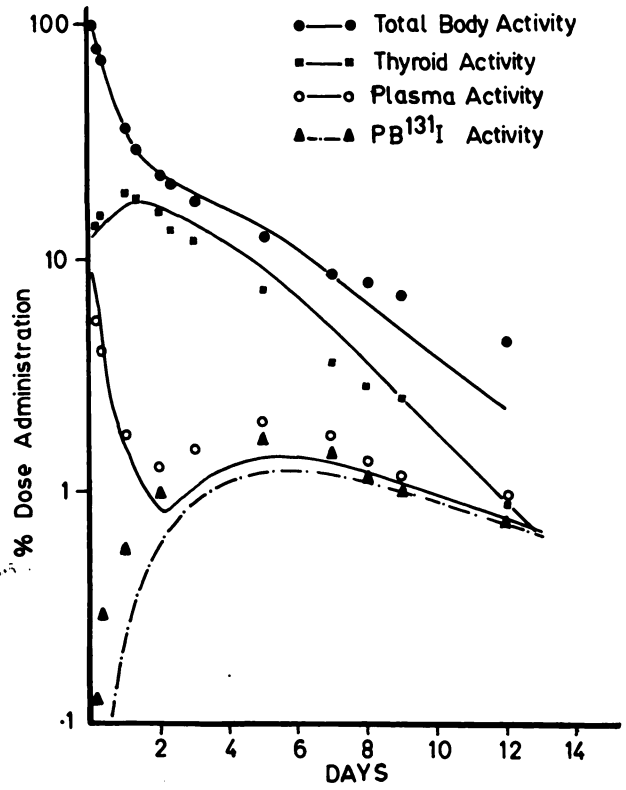

FIG. 2. Total-body retention, thyroid uptake, and plasma and protein-bound ^{131}I activity in patient treated with ^{131}I over period of 12 days. Points are experimental values and lines drawn are values predicted by model. Coefficient of correlation between observed values in all 16 studies and corresponding values predicted by model is 0.9906.

$T(t)/T(0)$ (the fractional functioning thyroid), L_{12} and L_{21} at various time intervals for the same study shown in Fig. 2.

The coefficient of correlation between the observed data points for all 16 patients studied and their corresponding values as given by the model is 0.9906 ($p < 0.001$). The equation of regression of the model value (Y) on the experimentally observed value (X) is

$$Y = 0.952\,X - 0.177 \qquad (7)$$

The standard deviations for slope (0.952) are 0.005 and for the intercept (0.177) are 0.146.

Table 1 gives the mean and standard deviations of the model parameters for all 16 patients studied.

Radiation dose delivered to the thyroid, total body, blood, and metastases is depicted in Table 2. Figure 4 shows the total thyroidal dose plotted against the maximum ^{131}I concentration per gram of thyroid tissue in the 16 patients with thyroid cancer. The maximum ^{131}I concentration was calculated by multiplying the dose administered and the maximum thyroid uptake expressed as fraction of dose admin-

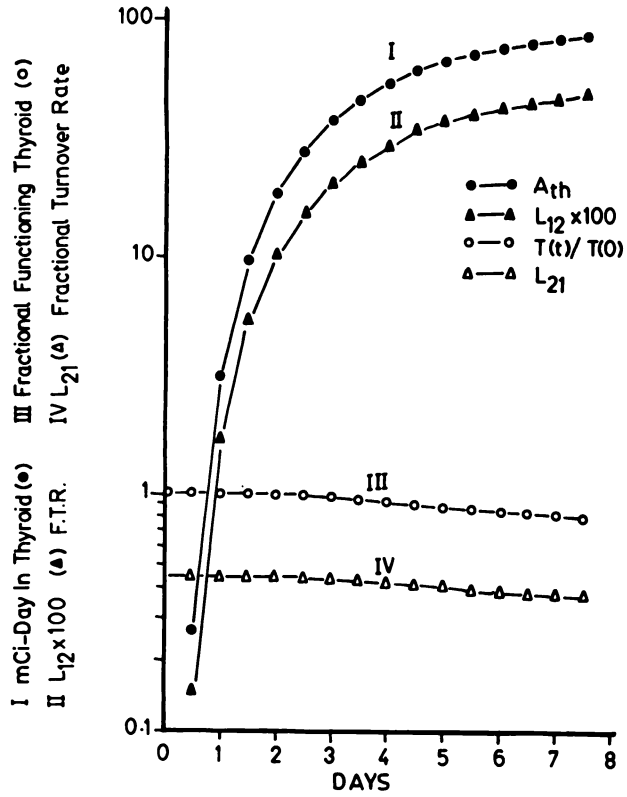

FIG. 3. Time-dependent variations in A_{th}, L_{12}, L_{21}, and T(t)/T(0) in same patient as shown in Fig. 2.

TABLE 1. MEAN AND STANDARD DEVIATIONS OF THE FRACTIONAL TURNOVER RATES (L_{ij}), FRACTION OF COMPARTMENT j SEEN IN SET OF OBSERVATION i, (S_{ij}), PBI SPACE, IODIDE SPACE, AND CONSTANT OF PROPORTIONALITY C_1 FOR 16 PATIENTS TREATED WITH ^{131}I

*L_{21}	(0.178 ± 0.348)	
*L_{12}	0	
L_{01}	1.362 ± C.317	
L_{00}	0.015 ± 0.0072	
L_{41}	0.227 ± 0.383	
L_{14}	0.207 ± 0.256	
L_{04}	0.049 ± 0.029	
S_{01}	0.048 ± 0.029	
S_{00}	0.929 ± 0.188	
$S_{14,1}$	0.003 ± 0.007	
$S_{14,5}$	0.794 ± 0.301	PBI space 3.15 ± 1.91 liters‡
S_{71}	0.096 ± 0.049	Iodide space 25.9 ± 5.18 liters
S_{75}	0.861 ± 0.260	PBI space 2.99 ± 1.69 liters
S_{81}	0.027 ± 0.026	
S_{84}	1.045 ± 0.133	
†C_1	0.014 ± 0.016	

* Rate constant before radiation damage.

† Constant of proportionality in Eq. 3 relating to the destruction of thyroid and the millicurie day in the thyroid.

‡ This value is slightly higher as compared with the corresponding value obtained by S_{75}, probably due to small losses of PBI radioactivity while precipitating with trichloroacetic acid. However, the difference is not significant ($P > 8$).

TABLE 2. TOTAL ABSORBED DOSE IN RADS

S (No.)	Dose administered (mCi)	Thyroid	Blood	Total body	Metastasis
1	90	1,380.7	36.2	21.1	
2	205	5,504.1	44.1	56.8	
3	230	66,000.4	90.8	101.3	
4	190	17,150.4	124.7	142.1	6,398.1
5	220	1,792.9	50.4	43.2	
6	200	6,425.5	40.2	51.6	
7	290	2,100.0	92.4	75.4	
8	110	62,531.5	108.0	114.6	
9	350	62,473.4	99.2	100.8	13,728.7
10	415	9,253.4	154.2	126.2	
11	215	220.9	84.3	65.3	
12	240	7,022.3	71.8	60.7	
13	95	17,656.1	29.1	32.8	
14	309	829.2	107.3	90.1	
15	109	108,152.2	54.4	60.2	
16	450	1,105.6	158.2	129.1	2,111.8
Mean		23,099.9	84.1	79.9	7,412.85

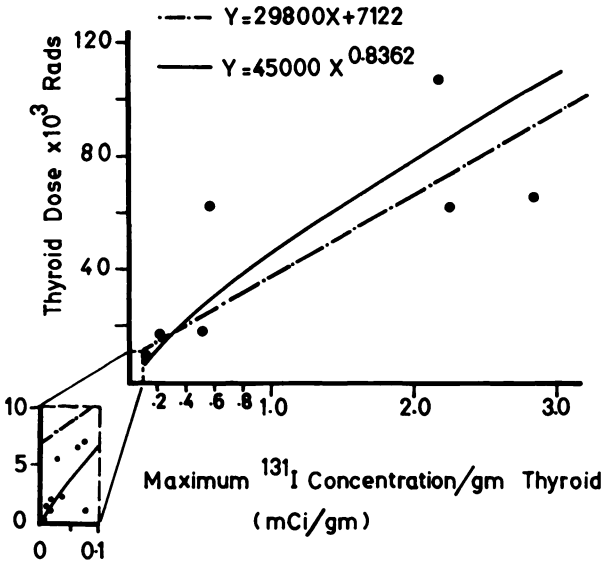

FIG. 4. Correlation between cumulative dose to thyroid over an infinite time and the maximum concentration of ^{131}I in thyroid. γ for the continuous curve is 0.934.

istered (compartment 2), predicted by the model and divided by the weight of thyroid in grams.

DISCUSSION

Berman, et al (*9,10*) have described techniques for kinetic analysis which are not only applicable to a steady-state system but can also be used for unsteady-state kinetics. After an unsuccessful attempt to fit our experimental data to a steady-state model, time-dependent variable fractional turnover rates between thyroid and plasma were introduced. The assumption is justified since an acute and a massive radiation dose to the thyroid does alter thyroidal

metabolism of iodine. The values for total-body radioactivity, thyroid radioactivity, plasma radioactivity, PBI radioactivity, and metastases radioactivity predicted by the model agreed well with the corresponding experimentally measured values in all 16 studies as shown by the correlation of 0.9906 and the equation of regression (7) which is not far away from the ideal line with slope 1.0 and intercept 0.0.

The variations in the turnover rates associated with thyroid uptake (L_{21}) and discharge of iodide from the thyroid (L_{12}) for 1 μCi of ^{131}I in a simulated model were negligible. In this case, L_{21} varied from 1.0 to 0.99985 and L_{12} varied from 0 to 0.0095 over a period of 10 days. The cumulative dose to thyroid, blood, and total body from 1 μCi of ^{131}I was found to be 1.039, 0.00043, and 0.00071 rads, respectively, over a 10-day period.

The variations in L_{21} and L_{12} in patients with thyroid carcinoma treated with a large ablation dose of ^{131}I were, however, significant. Figure 3 illustrates these variations in one of the patients treated with 109 mCi of ^{131}I. L_{12} varied from 0.0 to 0.442 and L_{21} from 0.447 to 0.353. A similar pattern of variation was observed in all 16 patients studied. The individual value of L_{21} (rate constant for thyroid uptake) varied from patient to patient which was due to different amounts of functioning thyroid tissue left after surgery. A high standard deviation of 0.348 for L_{21} (Table 1) confirms that the extent of thyroidectomy was variable from patient to patient.

Equations 5 and 6 show that changes in L_{12} are directly proportional to total millicurie day in thyroid, and L_{21} is proportional to fractional functioning thyroid remaining in the thyroid. Thus with large therapeutic doses of radioiodine, dose delivered to the thyroid would be less than the dose delivered had there been no variation in L_{12} and L_{21}. These time-dependent variations are suggestive of a possible saturation effect at higher concentrations of ^{131}I/gm of thyroid tissue. The constant of proportionality (C_1) showed marked variations from patient to patient (Table 1). The high standard deviation of 0.016 for the mean C_1 value of 0.014 is probably due to the difference in radiosensitivity of individual thyroid tissue or malignancy or both.

The line and the curve fitted on the least-square principle (Fig. 4) clearly indicates that the curve $Y = 45{,}000 \times {}^{0.8362}$ is a better representation of the observed data. Although the dose delivered to the thyroid appears to be linearly related to radioiodine concentration, a change of slope beyond ^{131}I concentration of 0.4 mCi/gm of thyroid can be made out which again indicates a possible saturation effect. However, more data with a higher radioiodine concentration per gram of thyroid tissue are needed to confirm this effect.

REFERENCES

1. BROWNELL GL: Analysis of techniques for the determination of thyroid function with radioiodine. *J Clin Endocrinol Metab* 11: 1095–1105, 1951

2. ROBINSON E, ROTBLAT J: An electrical analogue of the metabolism of iodine in the human body. *Br J Radiol* 28: 191–198, 1955

3. BERMAN M: Application of differential equations to the study of the thyroid system. *Proc 4th Berkeley Symp Math Statist* 4: 87–99, 1961

4. BERMAN M, HOFF E, BARANDES M, et al: Iodine kinetics in man. A model. *J Clin Endocrinol Metab* 28: 1–14, 1968

5. BERMAN M, WEISS MF: *Users Manual for SAAM*, PHS Publication No 1703, NIH, 1967

6. LOEVINGER R, BERMAN M: A schema for absorbed-dose calculations for biologically distributed radionuclides. MIRD Pamphlet No 1, *J Nucl Med* 9: Suppl No 1, 7–14, 1968

7. DILLMAN LT: Radionuclide decay schemes and nuclear parameters for use in radiation dose estimation. MIRD Pamphlet No 4, *J Nucl Med* 10: Suppl No 2, 7–30, 1969

8. BROWNELL GL, ELLETT WH, REDDY AR: Absorbed fractions for photon dosimetry. MIRD Pamphlet No 3, *J Nucl Med* 9: Suppl No 1, 27–39, 1968

9. BERMAN M, WEISS MF, SHAHN E: Some formal approaches to the analysis of kinetic data in terms of linear compartmental systems. *Biophys J* 2: 289–316, 1962

10. BERMAN M, SHAHN E, WEISS MF: The routine fitting of data to models. A mathematical formalism for digital computers. *Biophys J* 2: 275–287, 1962