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Estimation of Total Body Iodine Content in Normal Young Men

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Total body iodine content was estimated in six normal young men, who underwent ^{125}I balance studies during 64–92 days of daily ^{125}I administration. Total body retention of ^{125}I was measured as the difference between total administered ^{125}I and that collected in the urine and feces. Extrathyroidal ^{125}I was the difference between total and thyroidal ^{125}I content. The time-activity data for the ratio of extrathyroidal to total retained ^{125}I were fitted to a growth (inverse exponential) function. Fits of this growth function to the individual data sets yielded asymptotes, the equilibrium extrathyroidal/total ^{125}I ratios. The slopes of this function predicted the time that would have been required to achieve $^{125}I/^{127}I$ equilibration (approximately 10 months). Geometric mean for the asymptotic extrathyroidal/total ^{125}I ratio was 0.34 (range, 0.19–0.63), if it was assumed that measured urine and feces represented all of the ^{125}I lost to the body. If 90% measurement of ^{125}I loss was assumed, the geometric mean ratio was 0.32 (range, 0.17–0.60). Assuming that 90% of total loss is reflected in measured excreta and that total iodine content of the thyroid gland is 10 mg, geometric mean for total body iodine in these subjects was 14.6 mg (range, 12.1–25.3 mg).

Introduction

ALTHOUGH THE AMOUNT OF IODINE contained in the human thyroid gland is now fairly well established, there is little agreement about the amount in the other tissues and organs of the human body. In their recent Letter to the Editor in *Thyroid*, Venturi et al. (1) stated that: "In humans, the total amount of iodine is about 30–50 mg and less than 30% is present in the thyroid gland and in its hormones." Because this figure is much greater than some of the other published estimates for total body iodine (such as the 9.3 mg used by Riggs in his classic review [2]), a literature search for data on total body iodine in the human subject was performed. This search revealed little primary data, none reflecting modern laboratory methods. This led to an attempt to determine the relative steady state quantities of thyroidal and extrathyroidal iodine in normal human subjects. The data analyzed in this study were collected over 30 years ago, in an attempt to achieve total body $^{125}I/^{127}I$ equilibration, a goal that proved to be impractical. (As discussed below, complete equilibration would have required nearly a year of daily ^{125}I administration.) Other analyses derived from this study have been published elsewhere (3–5), and a full mathematical model analysis based on them is still planned.

Methods

Study protocol

Six healthy male college students, who were compensated for their participation, were studied between 1966 and 1968. Subjects were ambulatory during the study. Subjects 1 and 2 were not hospitalized. Subjects 3 through 6 were housed at the Clinical Research Center of the University of California, Los Angeles, Medical Center. There they received a constant iodine diet (identical weekly menus), but they were not confined to the hospital during waking hours. Subjects were studied in pairs. The weekly diet of one pair of subjects was homogenized and found to contain an average daily content of 600 μg iodine. None of the subjects had any change in dietary habits during the course of the study. All subjects gave written informed consent, and the study was approved by the local human studies and radiation use committees.

^{125}I-iodide was administered to the subjects in daily oral doses, the amount corrected back to the beginning of the study. For example, a nominal dose of 1 μCi (0.037 MBq) given on day 61, one ^{125}I half-life from the beginning of the study, would actually contain only 0.5 μCi (0.0185 MBq). This was accomplished by preparing capsules containing all

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of the daily doses for a given subject at the beginning of his study, each capsule containing the nominal daily dose at the time of preparation. Subjects received a 50 μCi (1.85 MBq) loading dose on day 1, followed by nominal daily doses of 1 μCi (0.037 MBq) per day for 64–92 days. Subjects 3 through 6 received 10 units of bovine thyrotropin (TSH) intramuscularly 24 hours prior to their loading doses. Use of a loading dose and of initial TSH stimulation were attempts to speed $^{125}I/^{127}I$ equilibration by providing a relatively large thyroidal tracer pool, analogous to the loading dose used in a primed infusion study. The 50:1 ratio of loading dose to daily dose, and the even greater ratio with TSH were based on an assumed thyroidal ^{125}I release rate of about 1%–2%/day.

Data collection was carried out throughout the period of daily tracer administration and for varying periods thereafter. Only the data from the tracer administration period of the protocols are considered in the present analysis.

Blood samples were obtained at intervals of 1–3 days. Serum was separated and the protein-bound portion containing the thyroid hormones was separated from radioiodide by dialysis under running water as previously described (4). Urine and feces were collected continuously during the study and processed as previously described (4). Aliquots of total serum, dialyzed serum, urine and feces were counted against an aliquot of the same standard solution used for measurement of thyroidal ^{125}I activity.

Thyroidal ^{125}I was measured daily for the first 1–2 weeks and three times a week thereafter. This measurement used a radioiodine uptake technique, with collimated sodium iodide crystal and a standard (10 μCi or 0.37MBq) in a specially designed Lucite phantom with a chamber molded from a human thyroid and an absorbing configuration mimicking the human neck. Thigh counts were used to correct for neck background. With this setup, we found in our clinical practice that ^{125}I thyroidal uptakes were similar to ^{131}I uptakes.

Daily values for thyroidal ^{125}I, total serum ^{125}I, and serum protein-bound ^{125}I were estimated by linear interpolation of adjacent values when measurements were made less frequently than daily. When urine and feces were measured in 5-day pools, daily values were estimated by dividing by 5. Cumulated excretion of ^{125}I in the urine and the feces were used in the analysis.

Corrections for systematic errors in the observed data

Three types of potential error were explored and corrected for:

1. Noncompliance of subjects with the requirement for complete collection of urine and feces.
2. Loss of ^{125}I from the body other than through urine and feces or systematic loss during the processing of samples.
3. Discrepancies between the actual ^{125}I content of the administered capsules and of the standards used for the thyroid, serum, urine, and feces measurements.

The noncompliance problem was handled by inspection of each subject's urine collection pattern during the period when excretion would be expected to be stable, that is, after the loading dose had been completely disposed of (approximately 3 days). Urine collections containing less than 80% of the average of the apparently complete collections were considered to be erroneous. They were replaced by the mean value for that subject's remaining urine collections. Approximately 30% of the samples were handled in this way. No such attempt at correction of the fecal collections was attempted, because they were not as stable as the urine collections and they contributed a relatively small portion of total ^{125}I excretion.

The question of possible external loss of ^{125}I from sources other than the collected urine and feces was handled by doing all analyses under two different assumptions: that 100% of loss to the body is accounted for in the measured excreta and the 90% of loss is accounted for in the measured excreta.

It became apparent that in some cases, there was a discrepancy between measurement of the ^{125}I doses and the standards used in the thyroid, serum, urine, and feces measurements. We noted that, sometimes, more ^{125}I could be accounted for than had been administered. While the reason for this discrepancy is uncertain, it seems likely that it is because the standard solution used for all of the experimental measurements was prepared separately from the concentrated solution used in the capsules administered to the subjects. A technical error leading to inappropriately low standard solutions seems most likely. To correct for this discrepancy, the activity in all known sites of ^{125}I was summed. This included ^{125}I in the thyroid, in the serum protein bound iodine pool (amount per liter $\times$ 9.4 [6]), in the iodide pool (amount per liter $\times$ 22.3 [7]), and in the cumulated urine and feces. The minimum of these values, several (6.3 ± 3.9) days after the beginning of the study, was assumed to equal the cumulated dose to that day. The ratios of this factor to the cumulated dose on that nadir day were used to correct the thyroid, serum, urine, and feces measurement. An example of the calculation of this correction factor (for Subject BI, whose nadir day was day 3) is:

Thyroidal ^{125}I content:	27.095 μCi
Plasma organic $^{125}I \times 9.4$	0.135 μCi
Plasma inorganic $^{125}I \times 22.3$	0.548 μCi
Cumulative urine ^{125}I	31.937 μCi
Cumulative fecal ^{125}I	0.213 μCi
Total ^{125}I accounted for	59.918 μCi
Total ^{125}I administered to date	52.000 μCi
Correction ratio	0.868

When 90% collection of excreta was assumed, the values for the urine and feces used in the calculation of this correction factor were divided by 0.9. The correction factors used averaged 0.92 ± 0.09 when 100% measurement of loss in the observed data for excreta was assumed and 0.86 ± 0.07 when 90% was assumed.

Data analysis

Percent of stable iodine in extrathyroidal spaces. Total retained ^{125}I was calculated for each day for each subject as the difference between the cumulated nominal ^{125}I dose to that day and the cumulated nominal ^{125}I in the corrected urinary and fecal measurements. The thyroidal ^{125}I on that day was subtracted to yield the nonthyroidal-retained ^{125}I. The ratio

of the nonthyroidal-retained ^{125}I to the total retained ^{125}I was expressed as the "percent in nonthyroidal spaces." This percentage was plotted as a function of time and fitted to a growth curve using the SAAM II numerical analysis program [8]:

$$y_t = y_{max} - y_{max} * \exp(-\text{slope} * t)$$

$$y_0 = 0$$

where y_t is the observed percent in nonthyroidal spaces on day t, y_{max} is the equilibration value for that percent, y_0 is its zero time value, and slope is the slope of the exponential growth curve in fraction per day.

All data points were included in the fitting process, even though the data do not in fact intercept zero at the zero time point. In all cases, there were early high points, presumably representing undistributed retention of the loading dose, but omitting these early high points had no significant effect on the final result.

Initially, fits were done separately for the data sets assuming 100% and 90% collection of excreta. Because the slopes from these two calculations for each subject were within one standard deviation or less of each other, combined fits were done with a single slope assumed for the two conditions. The results presented here are from these restricted calculations.

Time required to reach extrathyroidal $^{125}I/^{127}I$ equilibration

The half-life (days) for approach to the equilibrated value was calculated as ln(2)/slope. Because nine half-lives are required to arrive within 0.2% of an asymptote, this half-life was multiplied by 9 to estimate the time needed to reach virtually complete equilibrium.

Results

Percent of retained ^{125}I in the extrathyroidal spaces

The means of the individual subjects' data for the percent of retained radioiodine in the extrathyroidal spaces, assuming that measured excreta are 90% of total losses, are presented in Figure 1. The fitted growth curve is also displayed as a solid line. Similar curves resulted from all of the individual subjects' data fits, whether the data were derived assuming that 90% or 100% of total loss was measured. The asymptotes, slopes and half times for the individual subjects and for the mean data are presented in Table 1.

As expected, by correcting for an assumed 90% measurement of true loss to the system, the total amount of activity left was reduced, and this was reflected in the nonthyroidal portion of the iodine pools. However, this effect was modulated by the need to make the same correction in the nadir data used to calculate the correction for discrepancies in the standards, so that the differences in results with the two assumptions are relatively small.

In addition to the linear means and standard deviations of the individual parameters, the geometric means are shown in Table 1. These appear to correspond more closely to the parameters derived by solution of the mean data, in keeping with the expected logarithmic distribution of biological data.

Stable iodine content

Table 1 also shows estimates of extrathyroidal and total body iodine, assuming a thyroidal iodine content of 10 mg in normal subjects (9). Extrathyroidal iodine (90% excretion assumption) ranged from 2.1 to 15.3 mg, with a geometric mean of 4.6 mg, or a total body iodine of 14.6 mg.

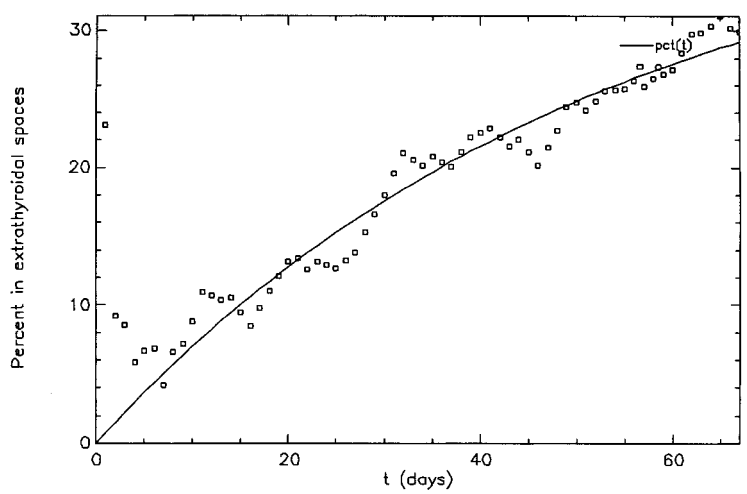

FIG. 1. The means of the individual subjects' data for the percent of total ^{125}I that was present in extrathyroidal spaces, fitted to a growth curve as described in the text. This particular data set incorporated the assumption that 90% of total loss of ^{125}I was reflected in the measured urine and feces. The fitted asymptote is 29.7%, corresponding to total body iodine of 14.2 mg, assuming that thyroidal iodine content is 10 mg. The slope, 2.22% per day, corresponds to 99.8% equilibration after 281 days. The use of a growth curve assumes that all of the tracer is in the thyroid at time zero. As can be seen here, and was seen in all of the individual studies, there is instead an early drop in the extrathyroidal tracer. This corresponds to the time required for uptake, distribution and excretion of the loading dose. The lowest point, when the largest percent of the total tracer is in the thyroid, was at 6.3 ± 3.9 days.

Table 1. Percent of Iodine in Extrathyroidal Spaces: Summary of SAAM II Fits

Subject	A	B	C	D	E	F	Mean	SD	Geom mean	Mean data[b]
Assuming that 100% of excreta are measured:										
% extrathyroidal	56.5	20.7	63.6	19.3	32.9	33.7	37.8	18.4	34.1	32.7
Estimated extrathyroidal iodine content (mg)[a]	12.9	2.6	17.5	2.4	4.9	5.1	7.6	6.2	5.2	4.9
Estimated total body iodine content (mg)[a]	22.9	12.6	27.5	12.4	14.9	15.1	17.6	6.2	15.2	14.9
Assuming that 90% of excreta are measured:										
% extrathyroidal	55.2	18.6	60.4	17.4	29.4	31.9	35.5	18.3	31.7	29.7
Estimated extrathyroidal iodine content (mg)[a]	12.3	2.3	15.3	2.1	4.2	4.7	6.8	5.6	4.6	4.2
Estimated total body iodine content (mg)[a]	22.3	12.3	25.3	12.1	14.2	14.7	16.8	5.6	14.6	14.2
Slope (%/day)	1.75	3.95	1.91	4.15	1.56	1.27	2.43	1.27	2.18	2.22
Half-life (days)	39.6	17.5	36.3	16.7	44.6	54.6	34.9	15.1	31.8	31.2
Time to reach 99.8% of equilibrium (days)	356	158	327	150	401	491	314	136	286	281

[a]Assuming thyroidal iodine content of 10 mg[9]
[b]Means of the subjects' data for each day, treated as though they were data for a subject.

Effect of TSH stimulation

Thyroidal 24-hour radioiodine uptake was 12.6% and 23.2% for subjects 1 and 2, who had no prior TSH stimulation. For subjects 3 through 6, each of whom received 10 units of bovine TSH 24 hours before the loading dose, it was 42.0% + 7.4%. However, this early thyroidal stimulation did not speed the eventual equilibration of the ^{125}I pools. The half times for equilibration were 39.6 and 17.6 days for subjects 1 and 2, and 36.2, 16.7, 44.6, and 54.6 days for the four TSH-stimulated subjects.

Discussion

It is surprising that the total iodine content of the human body remains uncertain after many years of interest in iodine metabolism. Thyroidal iodine content has been measured accurately by fluorescent scanning, and the estimate of 5–15 mg in the normal human thyroid [9] is now well established. Similar methods are not available for other tissues and organs. Salter's textbook [10] in 1940 quoted a figure of 10 to 50 mg for total body iodine, based on a 1928 German study (11). Riggs, in his 1952 review (2), estimated normal thyroidal iodine to be 8 mg and other iodine pools to total 1.3 mg. Hamolsky (12), in 1965, estimated total body iodine to be 9–10 mg, of which 8 mg is in the thyroid gland and only microgram levels in the skin, skeleton, and muscle. A prominent 1967 Italian physiology text [13], however, gave a figure of 50 mg for total human iodine content. This text assigned 10–15 mg to the thyroid, 10 mg to the bones and muscles, 5 mg to the epidermis, and 15 mg to the salivary glands and gastric mucosa. More recently, Delange and Ermans (14) estimated total body iodine to be 15–20 mg.

The present attempt to provide an independent measurement of the relative importance of the thyroidal and extrathyroidal iodine contents appears to be the first such effort. The only modeling approach to a similar problem of which the author is aware is a 1977 study by Smith and Edmonds (15). They found a slow component of inorganic iodide transport in athyreotic individuals, which became apparent in a 34-day period of observation. This compartment contains only about 0.004 mg iodine.

The period of ^{125}I administration in the present study was only 64–92 days, and Table 1 shows that some of 9 or 10 months would have been necessary to achieve isotopic equilibrium. Such a long period of study would have been impractical, so we are dependent on the projections from a simple model for our estimates of the relative importance of the extrathyroidal iodine pools.

There are other technical limitations to this study. Thyroidal iodine content was not measured in the individual subject. Indeed, the fluorescent scanning methodology was not yet available. Therefore, the estimates of extrathyroidal and total iodine provided depend entirely on an average thyroidal iodine content value derived from the study of other normal subjects by other investigators. There is a wide individual variation in the iodine content of the normal thyroid, and this can be expected to vary further with nutrition and disease.

The impact of incomplete collections of urine and feces is discussed above. The corrections applied to correct for them may have caused misleading results. To check for the quantitative importance of these corrections, solutions were also carried out without such corrections, assuming that subject compliance with collection of urine and feces was perfect. The resulting mean ± standard deviation for the percent in the extrathyroidal spaces was 48.5% ± 22.5%, as compared to 37.8% ± 18.4% for the solutions presented in Table 1, which reflect corrections for apparent noncompliance. Thus, although it is unfortunate that such corrections were necessary, their effect on the resulting projections is not dramatic.

It must also be remembered that the subjects for this study were normal young men on an iodine-rich diet (approximately 600 μg/d; the study was performed at a time when hamburger buns had iodine-containing preservatives). Their thyroid glands were clinically normal. All were of average build. Nothing is known of the effects on extrathyroidal iodine distribution of iodine loading or deprivation, of obesity or emaciation, of age or gender or of disease state. What effect conditions such as Graves' disease might have on the extrathyroidal iodine pool remains a matter of speculation.

Finally, these results need to be confirmed and expanded by direct biochemical measurement, using modern methods, of the iodine content in the various extrathyroidal tissues. Such analyses could elucidate not only the total iodine contents of the tissues, as studied here, but their biochemical patterns. The nature of the nonthyroidal iodine reported here

is unknown. Little is in the blood pool or in compartments that readily exchange with the blood pool. Taurog (personal communication, December 2000) has recently estimated the extrathyroidal iodine due to measurable thyroxine (T_4), triiodothyronine (T_3), reverse triiodothyronine (rT_3), Tetrac and iodide to approximate 1.1 mg. Using the geometric mean of 4.6 mg for total nonthyroidal iodine estimated in this study, some 76% of the total body iodine is unaccounted for by the usual measurements and short term models. If one considers only the active thyroid hormones, T_4 and T_3, which Taurog estimates at 0.8 mg total, this figure rises to 83%. It seems likely that most of this unaccounted-for iodine is in the form of thyroid hormone degradation products, in view of the study by Smith and Edmonds (15) that showed the slow inorganic iodide pool contained only a few micrograms. Nonspecific protein binding of iodine after hormone deiodination seems likely. In view of the wide individual variability in the amount of extrathyroidal iodine estimated in this study, it is unlikely that much of the iodine is in the form of active hormone within the tissues. Biochemical tissue analyses would provide a firm basis for current speculations about the relative importance of extrathyroidal iodide and thyroid hormone products to physiology and pathology.

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