Colonic Excretion of Iodide in Normal Human Subjects

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ABSTRACT

Patterns of fecal radioiodine excretion were studied in seven normal young men with intact, unblocked thyroid glands, who received repeated oral daily doses of \( ^{125}I \)iodide in an attempt to achieve isotopic equilibrium. Fecal radioactivity was assumed to have originated either in the circulating inorganic radioiodine (radioiodide) compartment or in the circulating hormonal protein-bound iodine (PBI) compartment. Activity in the PBI compartment was measured directly in serum samples from which radioiodide had been removed by dialysis or resin treatment. Activity in the radioiodide compartment was measured by the difference between total and hormonal radioiodine, and also as a projection from the rate of urinary excretion of radioiodine. These compartments were fitted to the observed sequential fecal radioiodine data in each subject to identify the origins of the fecal radioactivity, using the SAAM modeling program. The fraction of fecal radioactivity attributable to iodide was \( 0.55 \pm 0.35 \) (mean ± SD) (geometric mean 0.44, range 0.25-0.96). In all cases, at least some contribution from the iodide compartment was required for model fit to the observed pattern of fecal radioiodide excretion. These data demonstrate that, despite long-existing opinion to the contrary, iodide is an important component of intestinal iodine excretion in humans. This finding explains the presence of colonic activity in postradioiodide images of athyreotic patients.

INTRODUCTION

The distribution and peripheral kinetics of inorganic iodine (iodide) were extensively studied in the early years after \( ^{131}I \) became readily available, and the basic model for iodide in humans was established in a review by Riggs in 1952 (1). Evidence available from both human and animal studies led to the conclusion that oral iodide is quantitatively absorbed and that little or no iodide is excreted in the feces. The current prevailing precept is that fecal iodine has its origins exclusively in biliary excretion of the thyroid hormones. At least one modern text presents this view (2).

If all fecal iodine were indeed hormonal in origin, one would not expect athyreotic patients who have no sites of iodine organization to have any colonic radioiodide after radioiodide administration. Practical experience in the nuclear medicine clinic points to the contrary. It is not unusual for patients who have no other evidence of functioning thyroactive tissue to demonstrate radioactivity in the distribution of the colon (Fig. 1) on delayed total body radioiodide imaging studies. Such patients do not display hepatic radioactivity, as would be expected were their colonic activity the result of biliary excretion. Hepatic activity, when seen in this context, is regularly associated with the presence of thyroactive tissue (3,4). The colonic activity is generally not seen in early images, so it is unlikely to come from incomplete absorption of the oral dose. Probably, this colonic activity is the result of transport of radioiodide into the intestine from the mesenteric circulation.

The present study examines the origin of fecal radioiodine, applying modern mathematical modeling methodology to data collected over 20 years ago. The original purpose of the study for which the data were collected was to achieve total body equilibration between \( ^{125}I \) and \( ^{131}I \), in order to infer \( ^{127}I \) distribution from \( ^{125}I \) distribution. The goal of complete equilibration was not met: Decay-corrected thyroidal and serum radioactivities did not become completely stable despite prolonged periods of tracer administration. The data have previously been presented only in abstract form (5). Further analysis of this data set is in progress.
FIG. 1. $^{131}I$ whole body image of an athyreotic man with thyroid cancer, showing obvious colonic activity. This scan was made 3 days after oral administration of 2 mCi of $^{131}I$ iodide. The patient’s serum at the time of the scan contained no hormonal radioactivity.

MATERIALS AND METHODS

The data analyzed were obtained from seven healthy young male college students between 1965 and 1968. Subjects were ambulatory during the study (45 to 171 days). Four of the subjects were housed at the Clinical Research Center of the University of California, Los Angeles, Medical Center on a constant iodine diet (identical weekly menus), but were not confined to the hospital during their waking hours. The other three subjects ate their normal diets at home. None of them had any change in his usual dietary habits during the course of his study. All subjects gave 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 activity at the beginning of the study. [For example, a nominal dose of 1 μCi (0.037 MBq) given on day 61, one 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 of the daily doses for a given subject at the beginning of his study, each capsule containing the planned nominal daily dose at the time of preparation. Subject 1 received a nominal daily dose of 3 μCi (0.111 MBq) for 41 days. The other subjects received 50 μCi (1.85 MBq) loading doses on day 1, followed by nominal daily doses of 1 μCi (0.037 MBq) per day for 64–92 days. Data collection was carried out throughout the period of daily tracer administration and for varying periods afterward. Subject 3 had no fecal collections after termination of the daily tracer doses. Subject 1 continued fecal collection for only 4 days after $^{125}I$ doses were terminated, and subject 5 for only 5 days. The other four subjects continued full data collection, including fecal collections, for 30, 40, 50, and 60 days, respectively, into the decay period after termination of the daily tracer doses.

Blood samples were usually obtained just before the daily dose of $^{125}I$, at intervals of 1–3 days. In some cases, for practical reasons, serum sampling and the daily tracer dose were not paired, so that their temporal relationship is not certain in all cases (see below). Unfortunately, no permanent record was kept of such discrepancies.

Serum was separated, aliquoted, and the protein-bound portion containing labeled thyroid hormones (PBI) was separated from radioiodide by dialysis under running water for 24 h (subjects 2–7). Subject 1's serum iodide and PBI were separated by passing the sera through Amberlite IRA 400 resin instead of by dialysis. Using the dialysis method, less than 1% of added radioiodide and over 99% of added purified radioactive T$_4$ were retained in the PBI fraction. For the resin method used for subject 1, these values were approximately 5 and 95%.

Twenty-four-hour urine collections were aliquoted and their total volume recorded. In the four subjects studied in the Clinical Research Center, feces were collected in 5-day pools, homogenized, aliquoted by weight and total weight recorded. The other three subjects' feces were counted individually as described below and the data pooled in 5-day segments.

Aliquots of whole serum, dialyzed serum (subjects 2–7) or resin effluent (subject 1), 24-h urine collections, and also of the homogenized 5-day fecal collections from subjects 4–7, were counted in a well counter attached to a gamma spectrometer and compared with counts of a standard aliquot of the daily $^{125}I$ dose.

Each individual fecal sample from subjects 1, 2, and 3 was counted in its original container, using a thyroid uptake probe attached to the same gamma spectrometer used for the well counting. A standard geometry was maintained for these counts. Counts of the fecal samples were compared with counts from a standard diluted in sawdust and counted in the same geometry as the fecal sample. Results, expressed as μCi/sample, were combined in 5-day sums. There was no systematic difference between the 5-day fecal $^{125}I$ content measured by the two methods.

Five-day fecal excretion data were divided by five to calculate the mean daily fecal excretion for each 5-day period. For purposes of the model solution, the timing of each fecal or urine collection was considered to be at the midpoint of the collection period.

Because all $^{125}I$ counts, including those in the counting standards and in the daily tracer doses, as well as those from the subjects' thyroid, sera, and excreta, decayed at the same rate, the process of radioactive decay did not affect the approach to equilibrium. All counts were expressed as μCi/L of serum or μCi excreted/day, as of the beginning of the study.

Initially, serum $^{125}I$ inorganic iodine (iodide) data for use in the mathematical model were obtained from the difference between total $^{125}I$ activity and $^{125}I$ PBI activity. However, this is the difference between two observations each of which is subject to biological and experimental variation. The resulting calculated values showed marked variability. In addition, in most cases, this value represents serum radioiodide 24 h after the most recent dose of $^{125}I$, whereas the value needed for clearance measurements is the average serum radioiodide concentration for that day, the area under the radioiodide time–activity curve for 24 h, expressed in μCi-h/24. For these reasons, in the final analyses, as a substitute for direct measurement, serum radioiodide was projected from the daily urine cumulative $^{125}I$ content.
This projection used the observation that the mean urinary clearance for radioiodine in a similar group of subjects (6) was 34 ml/min, or 49 L/day. This is another way of stating that the daily urinary radioiodine excretion, in μCi/day, is 49 times the mean serum radioiodine in μCi/L. To project the mean serum radioiodine for a given day, the cumulative urinary radioiodine for that day was divided by 49. Serum radioiodine values projected in this manner were 2.5 ± 1.2 times the measurements made from the difference between total serum and serum PBI counts 24 h after the most recent tracer dose. This corresponds to a serum disappearance half-time for iodide of 10.3 h, a rate slower than the 6-h half-life observed in a similar group of young men in the same laboratory (6). Riggs (1) and Berman (7) also reported human iodide disappearance half-life to be about 6 h. A 6-h disappearance half-life would lead to a ratio between serum iodide calculated by the two methods used here of 5.4, rather than the 2.5 ratio observed. This discrepancy could be due to short periods of observation after tracer injection in the studies quoted (1,6,7), so that a late flattening of the iodide disappearance curve would have been missed. It could also be due to incompleteness of the urine collections in the present study, but that would not be sufficient to explain the discrepancy: During the final 2 weeks of tracer administration, when tracer excretion might have been expected to approach tracer intake, combined urinary and fecal radioactivity was 88 ± 9% of the daily tracer dose (geometric mean 87%, range 75–101%). The most likely source of the discrepancy is from irregularities of timing of the serum samples, with some of the samples drawn after < 24 h, when serum radioiodine values would have been above their 24-h minima. Because of this irregularity and because of the apparent relative reliability of the urine collections, the serum radioiodine values calculated from urine radioiodine excretion were used in the model solutions.

**Modeling methodology**

Modeling was done with the SAAM program (8), using a simplified conceptual model for iodide kinetics (Fig. 2). The QL technique (9), was used in the model solution. This technique allows one to project observed data directly into a compartmental continuous function which can be used as a forcing function in the model, without the need for previous curve fitting. This is done by making linear connections between the observed data points. Compartments for serum radioiodine and serum PBI were derived in this way and then fitted to the observed data for fecal excretion, to determine the fraction of each serum compartment which is reflected in the fecal excretion pattern, using the computational model shown in Fig. 3. This model fit calculated the fractions of each of the two serum radioiodine compartments (iodide and PBI) reflected in the fecal time–radioactivity curve. Since the serum data are in μCi/L of serum and the fecal data are in μCi/day, these fractions directly reflect the fecal “clearance” from each serum compartment, in L/day. Since the concentration of radioactivity in the PBI fraction of the serum was not the same as that in the iodide fraction, it was necessary to correct these clearance values for serum concentration differences in order to assess the actual fraction of fecal radioactivity originating from the serum iodide and PBI compartments. This correction was made using the fraction of radioactivity from iodide and from PBI in the subject’s serum during the later 125I intake portions of the subject’s study, when these fractions were stable.

**RESULTS**

Data for mean daily fecal radioiodine excretion from sequential 5-day fecal collections are shown as discrete triangles in Figs. 4 and 5, which present data from two subjects, one with primarily iodide clearance, the other with primarily PBI clearance. Also shown are the model fits to these data and the relative contributions of the two serum radioiodine compartments. Table 1 summarizes the results for the entire group of subjects.
FIG. 4. Fecal excretion (μCi/day) for subject 4, in whom the calculated radioiodide contribution was 17% of total fecal radioactivity. When the model was solved without the late post-¹²⁵I intake data, this contribution was 18%. Discrete triangles are the observed daily fecal excretion values; i.e., they are one fifth of the radioactivity in the 5-day fecal excretion periods. Data are shown at the midpoints of the 5-day fecal collection periods. The top solid line is the least-squares fit to these data using the model shown in Fig. 3. The lower lines represent the model partition of the total fecal radioactivity into iodide and PBI segments, as marked. The upper line is the sum of the other two lines.

Clearance into the feces from both the radioiodide and the radioactive PBI compartments varied widely among the subjects, and the relative contribution of the serum radioiodide compartment to total fecal radioactivity ranged from 17 to 96%. In none of the subjects could the fecal excretion curves be fitted satisfactorily from the reflection of the serum PBI compartment alone.

Since colonic transport rates vary among normal individuals, some subjects might be expected to show a time lag between serum radioactive iodide and PBI and their appearance in the feces. To examine this possibility, the model was solved for each subject with a sequence of possible time lags from 0 to 2.5 days. The sums of squares for the various model fits were examined, and the time lag producing the lowest sum of squares was chosen for each subject. This lag was 0.83 ± 0.69 days, a value consistent with the concept that much of the fecal radioiodine originates from secretion into the colon.

FIG. 5. Fecal excretion (μCi/day) for subject 7, in whom the calculated radioiodide contribution was 95% of total fecal radioactivity. This subject's data collection was continued only 7 days after ¹²⁵I intake was terminated. Symbols are as in Fig. 4.

DISCUSSION

In his comprehensive review of human iodine metabolism published in 1951 (1), Riggs summarized the existing literature with the statement that "only minute traces of iodide ion escape from the feces." This opinion has been carried over into a general belief, still current (2), that essentially all fecal iodine is of hormonal origin. However, other studies have indicated that some iodide is excreted through the gut. Oddie and coworkers (10), studying five anephric patients with unblocked thyroid glands for 4 days after a bolus administration of radioiodide, found fecal iodide clearance to be 3.580, 158, 778, 683, and 3.105 ml/day (mean 1.661 ml/day, geometric mean 986 ml/day). These clearances are in the same order of magnitude as the mean 614 ml/day (geometric mean 442 ml/day) observed in the present study. Oddie et al. expressed the opinion that fecal iodide clearance in their anephric subjects was increased over normals, and the author’s recalculation of data from an earlier study from this same group (11) indicates a fecal iodide clearance of about 370 ml/day during the first day or two after radioiodide administration to eight normal subjects.

Belshaw and coworkers (12), studying dogs given radioiodide with blocked thyroid glands and studied for 14 days after a bolus dose of radioiodide, found that transport from the central compartment to the feces averaged 0.067/day, or 6.6% of total excretory loss. This proportion is greater than was seen in the present human series, in which fecal radioiodide clearance averaged 1.2% of the total excretory clearance. This difference is most likely due to species differences, but it could also reflect the major differences in experimental protocol between the two studies.

Direct studies of the chemical nature of fecal radioiodine are difficult technically, although DiStefano (13) has applied his extraction method to the study of rat colonic contents and feces, with the conclusion that fecal radioiodide after labeled thyroid
hormone administration is less than 7% of total fecal radioactivity. The author has applied DiStefano’s (13) method to analysis of feline gut contents after equilibration with radioactive thyroid hormones, and has found that the colon contains much radioiodide, the relative concentration of which decreases distally (14). The latter finding suggests that, in the cat as well as the rat (15), iodide absorption by the colon is efficient. Presumably, the same is true of the human colon. Direct iodide secretion into the colon has been demonstrated in the rat (15), and it seems reasonable to assume that it occurs in humans as well. The radioactivity seen in the colons of some athyreotic patients on total body radioiodine scans (as in Fig. 1) is most likely due to this secretion. The amount of radioiodine actually present in the colon in any individual is a balance between the rate of iodide secretion and the efficiency of reabsorption. In normal subjects, such as those studied here, colonic activity also contains labeled organic iodide, the balance between biliary and intestinal secretion of labeled thyroid hormones and their reabsorption.

As noted above, three of the subjects had little or no data collection in the period after termination of [125I] intake. The question arises whether the lack of this information about the "tail" of the fecal data is important to the results. To examine this question, the model solutions for the four subjects with extensive "tail" data were repeated, omitting all fecal data after the first full collection period after termination of [125I] intake. The resulting values for clearances to feces from the iodide and PBI compartments were 115 ± 21% and 96 ± 17%, respectively, of the values calculated using all of the available data. It appears that most of the information needed for the model solution is contained in the portions of the data obtained before the end of [125I] intake.

The present study clearly demonstrates that fecal excretion of iodide does occur in normal young men, and that in some persons the iodide compartment is the major source of fecal radioiodine excretion.

ACKNOWLEDGMENTS

The author thanks Kim N. Diezeraad for expert technical assistance. The staff of the U.C.L.A. Clinical Research Center were uniformly supportive of this study, and the hospitalization of the subjects was supported by the CRC grant in effect during 1967 and 1968. The data collection was also supported by U.S.P.H.S. Grant R01 AM 09185. The modeling study was supported by DVA intramural medical research funds (Program 821).

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