Radiation Dosimetry of Radioiodinated Thyroid Hormones

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A physiologically based compartmental model for T_4 and T_3 metabolism in man was used to generate time-activity curves for residence of radioiodine in key organs. T_4 and T_3 labeled with ^{123}I, ^{124}I, ^{125}I, and ^{131}I were studied. Conditions modeled included radioactive iodine uptake (RAIU) values of 0%, 1%, 5%, 15% and 25%, and RAIU of 15% combined with various degrees of pharmacologic block of thyroidal RAIU. Using the MIRD "S" tables, rad doses were generated for each condition. While the shapes of the time-activity curves varied widely with alterations in physical and biological turnover and with changes in steady-state due to iodine administration, it was possible to calculate overall effective half-lives for each organ of interest from the integral of the time-activity curve projected by solution of the model. This overall effective half-life of the hormone for the body's exchangeable hormone compartments correlated well with calculated radiation dose to the thyroid in the unblocked state. With progressive degrees of iodine block, this correlation persisted, though with proportionately reduced thyroid radiation doses. Use and manipulation of a compartmental model, rather than the usual multiexponential model, for radiation dosimetry facilitates conceptualization and the projection of the effects of interventions such as iodide block.

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The radioiodinated thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) may be used in clinical evaluation though their major human use is in research settings. Presently, only the iodine-125- (^{125}I) labeled hormones [^{125}I]T_4 and [^{125}I]T_3, are commercially available routinely, but [^{131}I]T_4 and [^{131}I]T_3 can now be obtained by special order, and the ^{123}I-labeled hormones are under development. All of these must be processed for chemical purity, sterility, and freedom from pyrogens before parenteral administration to human subjects.

Since the primary metabolic disposal route for both T_4 and T_3 is deiodination, which converts the radioiodine to its iodine form, the radiation dosimetry of these compounds is complicated by thyroidal iodine metabolism. Calculation of the needed "μc-hour" integrals for application of the MIRD "S" tables (*1*) require a simulation model incorporating the known physiology of both the hormone to be studied and of iodide. The hormones are secreted in the bile, so their intestinal residence must also be accounted for; when they are given orally this is a major pathway. When the physiology is not in steady-state, as after a single blocking dose of stable iodine, which disappears before the hormone is fully metabolized, the simulation must include these changes. This paper presents the results of such a simulation.

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MATERIALS AND METHODS

The physiologic model used is presented in Fig. 1. The parameters shown are those assumed in the case of T_4 administration to a subject with an unblocked thyroid and 15% radioactive iodine uptake (RAIU).

The parameters of this model were taken primarily from previous work in this laboratory (*2,3*). Thyroidal release of radioiodinated hormone was adopted from the MIRD Dose Estimate Report for the radioiodines (*4*). Because this recirculation has a very small influence on dosimetry, we simplified the model by having

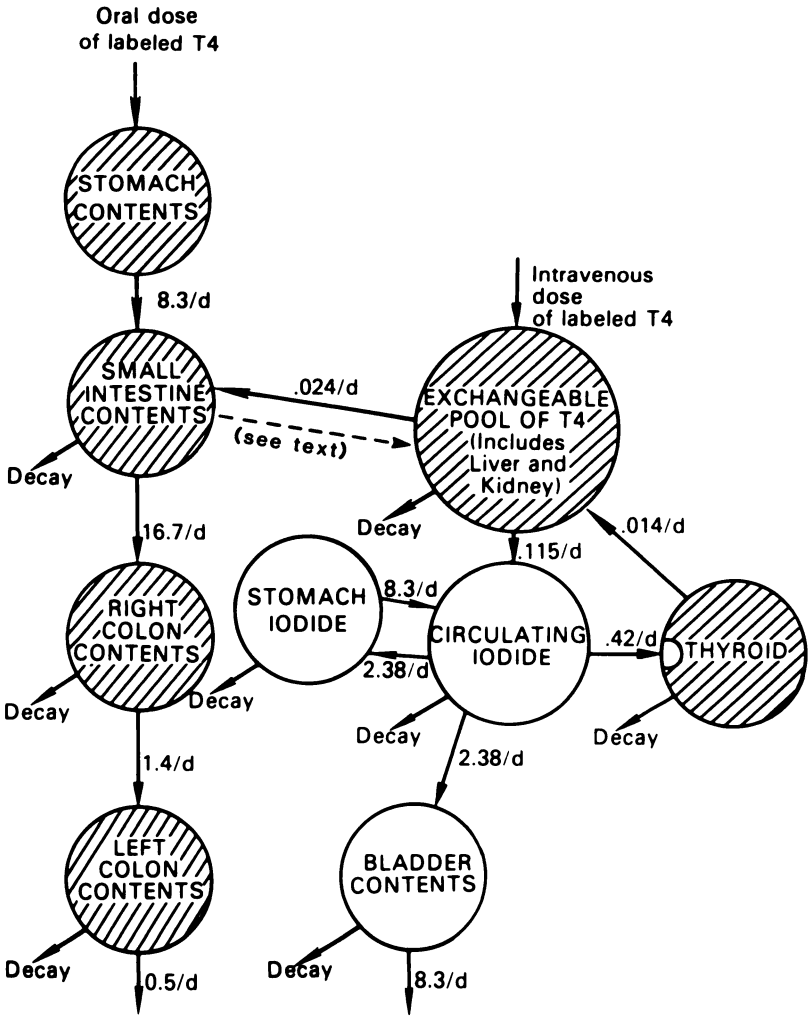

FIGURE 1
Simplified model used for dose calculations in this paper. In the figure, those compartments in which radioiodine is in iodide form are unshaded. Those compartments containing label in hormone form are shaded. Parameters shown are for T_4, with 15% RAIU, and the faster of the two iodide turnover rates studied. Same model structure, with parameter changes, applies for T_3. For the unabsorbed fraction of the dose after oral administration, the input function is into stomach; for i.v. dose or the absorbed portion of oral dose, input is into exchangeable pool

all thyroidal release into the hormone pool of interest. Excretion pathways are assumed to be 83% through deiodination and subsequent renal excretion, and 17% through biliary excretion of hormone conjugates (*5*). These ratios are reflected in partition of the exit from the exchangeable hormone pool into the intestinal hormone pool and into the serum iodide pool. Because reabsorption of hormone after biliary excretion as conjugates is quantitatively small, the model was simplified by omitting this reabsorption. On the other hand, after oral administration of the thyroid hormones, absorption varies in efficiency and must be taken into account. In this study, orally administered hormones are treated by partition into absorbed and unabsorbed fractions. The absorbed fraction is entered into the model as an intravenous injection; the unabsorbed fraction is shown in simple transit through the gastrointestinal tract. When the absorption fraction is unknown, 70% absorption of T_4 (*6*) and 90% absorption of T_3 (*7*) are reasonable estimates to use for subjects with normal gastrointestinal function.

As iodide secretion into the stomach is comparable to its appearance in the urine (*3*), these were set equal, again to simplify the model calculations. The rate for stomach emptying of either iodide or hormone is assumed to be 8.3/day. Since iodide is promptly absorbed after entering the small intestine (*3*), the process is simplified by showing the iodide transport directly from the stomach to the circulating iodide pool at the rate of stomach emptying (8.3/day). True gastric iodide absorption, probably negligible (*3*), is ignored. Values for transport within the gastrointestinal tract were estimated after consultation with a gastroenterologist, based on clinical observations. They are obviously subject to major variations among individuals and in different clinical settings.

Because of the rapid equilibration of liver and kidney with the circulating hormone pools, the simulation model incorporates them within a single large exchangeable compartment, and biliary excretion is obtained from it. The fractions of the exchangeable hormone pools assumed for liver and kidneys were calculated by assuming that all of the "fast" T_4 or T_3 distribution compartment (*2*), including the fraction of

the "instantaneous" compartment for T_3 that is excess over that for T_4 and albumin, is contained in the liver and kidneys. Partition between liver and kidneys of this fast compartment was based on organ size (*1*). The fractions of the exchangeable hormone pool used in the model solution, for T_4 and T_3, respectively, were 0.395 and 0.210 for liver and 0.0622 and 0.0331 for the two kidneys.

In addition to the distinct differences incorporated in partition of the exchangeable hormone compartment between T_4 and T_3, the only other difference was in hormone disappearance rate, the sum of deiodination, and of biliary secretion. For T_4, this value was taken as 0.139/day; for T_3, as 0.934/day (*2*). The figure used for T_3 incorporates the slight retarding effects of iodoprotein appearance on overall T_3 radioiodine disappearance.

As is customary in studies of thyroid hormone kinetics, parameters of the model are presented as fractions per day. Results were then converted to hourly rates, to conform with the S table method.

This model was used to generate time-activity curves for each of its compartments under the various conditions studied. Modeling was done using the SAAM 27 program (*8*), in its interactive version, Consam (*9*), on a VAX 11 computer. Simulations were carried out until the integrals of the respective compartments had been stable within 0.1% for a double-time period (e.g., the 120 and 240 day integrals were within 0.1% of each other). The integrated activities for the organs simulated by the model were then multiplied by the values for rads/μc-hr in the relevant S tables (*1*) and summed.

In preparing the S tables for use in these calculations, it was necessary to project the influence of those organs and tissues not modeled directly. These "Other Tissues" are widely distributed tissues. They are more inclusive than the "Other Tissues" of the S tables (primarily bone) and less inclusive than the S table "Whole Body". Hence S values assumed for "Other Tissues" in these calculations were interpolated linearly, by proportional weights of the organs not specifically accounted for, between the S tables for "Other Tissues" and for "Whole Body". Values assumed were for ^{123}I, ^{124}I, ^{125}I, and ^{131}I, respectively. For bladder wall as target organ, the values were 3.1, 18.0, 1.3, and 8.4 rads/uc hr × 10-6. For organ stomach wall as target, the values were 2.8, 16.0, 1.2 and 7.9; for small intestinal wall, 3.1, 18.0, 1.3, and 8.1; for right colonic wall, 3.0, 18.0, 1.3, and 8.2; for left colonic wall, 3.0, 19.0, 1.3, and 8.3; for kidneys, 2.7, 16.0, 1.3, and 7.9; for liver, 2.6, 14.0, 1.2, and 7.5; for red bone marrow, 3.7, 16.0, 2.0, and 8.0; for ovaries, 3.3, 19.0, 1.4, and 8.6; for testes, 2.2, 16.0, 1.0, and 7.1; for thyroid, 2.4, 15.0, 1.3, and 7.1, and for total body, 3.0, 18.0, 1.6, and 9.9 rads/uc hr × 10-6.

The simulation of the results of blocking doses of 500 mg iodide (from the usual ten drops of SSKI) was based upon the assumptions that a daily dose containing 10 mg iodine or more will block uptake (*10*), but that thereafter the trap is partially suppressed (*11*), and gradually recovers. One week of 50% suppression was used to model this partial suppression. To determine the circulating iodine remaining after a single 500 mg dose as elemental iodide, we ran the model with this dose as input into the iodide compartment. This simulation showed that the 10 mg level was reached at ~1.4 days. Therefore, we can no longer assume complete blockage after 2 days. On the other hand, when we ran the simulation with iodine turnover reduced to 0.5/day, which may be more typical of iodine deprivation (*12*), the results suggested complete blockade for 9 days.

Three conditions of iodine blockade were then studied, all for an iodine block in a person whose usual RAIU is 15%:

a. SSKI # 1: RAIU 0% for 2 days, 7 ½% for 7 days, then back to 15%. This condition models a single dose of 10 drops SSKI in a person with normal iodide turnover of 2.8/day.

b. SSKI # 2: RAIU 0% for 9 days, 7 ½% for 7 days, then back to 15%. This condition models 1 wk of blockade, ten drops of SSKI given every second day, in subjects who have normal iodide turnover. It also models a single dose in a person with iodide turnover reduced to 0.5%/day.

c. SSKI # 3: RAIU 0% for 16 days, 7½% for 7 days, then back to 15%. This condition models 2 wk of SSKI with normal iodide turnover or 1 wk when reduced.

To calculate dose from the unabsorbed portion of radioiodinated substances given orally, the model was run with the radioactivity input into the stomach. As no absorption with subsequent recirculation is assumed here, the results are identical for any nonabsorbed, nonmetabolized oral radioiodinated material. In the case of oral thyroid hormones that are partially absorbed, the absorbed portion is introduced into the exchangeable hormone pool of the model.

RESULTS

Dose calculations resulting from application of this model to the MIRD S Tables, for i.v. radioiodinated T_4 and T_3, in rad/mc, are presented in Table 1. The integrated simulated activities (as uc-hr each uc administered), on which these calculations were based, for the various organ systems and conditions modeled can be obtained from the author on request.

Illustrative time-activity curves, demonstrating the effects of the various conditions modeled, all for a normal person with RAIU of 15%, are presented in Figs. 2 and 3. Figure 2 shows that, compared with T_4, there is relatively rapid disappearance from the circulating pool of T_3, with a more rapid appearance of label

TABLE 1

Calculated Radiation Dose (rads/mc) Delivered After Intravenous Administration of Radioiodinated T_4 or T_3

	Rads/mc from i.v. T_4							Rads/mc from i.v. T_3						
Target	No RAIU	5% RAIU	15% RAIU	25% RAIU	SSKI #1 15% RAIU	SSKI#2 15% RAIU	SSKI#3 15% RAIU	No RAIU	5% RAIU	15% RAIU	25% RAIU	SSKI#1 15% RAIU	SSKI#2 15% RAIU	SSKI#3 15% RAIU
^{123}I														
Thyroid	0.04	0.23	0.65	1.06	0.14	—	—	0.03	0.92	2.70	4.49	0.32	—	—
Left colonic wall	0.07	0.07	0.07	0.07	0.07	—	—	0.19	0.19	0.19	0.19	0.19	—	—
Liver	0.56	0.56	0.56	0.56	0.56	—	—	0.21	0.21	0.21	0.21	0.21	—	—
Red bone marrow	0.06	0.06	0.06	0.06	0.06	—	—	0.05	0.05	0.05	0.05	0.05	—	—
Ovaries	0.04	0.04	0.04	0.04	0.04	—	—	0.07	0.07	0.07	0.07	0.07	—	—
Testes	0.02	0.02	0.02	0.02	0.02	—	—	0.03	0.03	0.03	0.03	0.03	—	—
Total body	0.06	0.06	0.06	0.06	0.06	—	—	0.05	0.05	0.05	0.05	0.05	—	—
^{124}I														
Thyroid	1.38	65.87	196.70	328.31	124.64	49.85	6.60	0.46	121.46	365.63	612.45	102.21	11.06	0.35
Left colonic wall	6.32	6.32	6.33	6.34	6.33	6.32	6.32	10.33	10.35	10.40	10.44	10.35	10.33	10.33
Liver	15.20	15.22	15.27	15.32	15.24	15.22	15.20	2.54	2.55	2.57	2.60	2.55	2.54	2.54
Red bone marrow	1.19	1.21	1.24	1.28	1.22	1.21	1.19	0.60	0.63	0.69	0.74	0.62	0.60	0.60
Ovaries	1.53	1.53	1.52	1.52	1.53	1.52	1.52	1.35	1.35	1.35	1.35	1.35	1.35	1.35
Testes	0.86	0.86	0.86	0.85	0.86	0.86	0.86	0.51	0.51	0.51	0.50	0.51	0.51	0.51
Total body	1.65	1.69	1.78	1.86	1.73	1.68	1.66	0.70	0.77	0.92	1.08	0.76	0.70	0.70
^{125}I														
Thyroid	0.26	110.14	345.15	602.06	272.36	156.58	54.68	0.05	117.90	370.76	649.12	119.91	16.35	0.06
Left colonic wall	1.81	1.84	1.93	2.02	1.90	1.86	1.83	1.84	1.88	1.97	2.07	1.88	1.84	1.84
Liver	3.46	3.53	3.70	3.87	3.65	3.57	3.50	0.32	0.32	0.34	0.36	0.32	0.32	0.32
Red bone marrow	0.26	0.28	0.31	0.34	0.30	0.28	0.27	0.09	0.10	0.13	0.15	0.10	0.10	0.09
Ovaries	0.26	0.27	0.28	0.29	0.28	0.27	0.27	0.18	0.18	0.19	0.20	0.18	0.18	0.18
Testes	0.10	0.10	0.10	0.11	0.10	0.10	0.10	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Total body	0.30	0.37	0.50	0.66	0.46	0.39	0.33	0.08	0.14	0.28	0.43	0.14	0.09	0.08
^{131}I														
Thyroid	1.17	131.84	397.42	666.81	280.94	132.57	27.78	0.28	195.38	592.07	997.04	177.53	21.55	0.19
Left colonic wall	7.46	7.48	7.53	7.58	7.51	7.48	7.46	10.43	10.48	10.58	10.58	10.48	10.44	10.43
Liver	13.19	13.24	13.33	13.44	13.29	13.24	13.20	1.71	1.72	1.74	1.77	1.72	1.71	1.71
Red bone marrow	0.75	0.76	0.80	0.83	0.78	0.76	0.74	0.31	0.33	0.37	0.42	0.33	0.31	0.31
Ovaries	0.89	0.89	0.89	0.90	0.89	0.89	0.89	0.65	0.65	0.65	0.66	0.65	0.65	0.65
Testes	0.50	0.50	0.50	0.51	0.50	0.50	0.50	0.24	0.24	0.24	0.24	0.24	0.24	0.24
Total body	1.22	1.28	1.40	1.52	1.35	1.28	1.23	0.40	0.49	0.66	0.84	0.48	0.41	0.40

Note: For brevity, values for bladder wall, stomach wall, small intestinal wall, right colonic wall, and kidneys are omitted. In each case modeled, absorbed dose by these organs was less than that for the liver and/or the left colonic wall. SSKI #1 simulates a single dose of 500 mg iodine and normal iodide turnover. SSKI #2 simulates 1 wk block with normal turnover or a single dose with reduced turnover. SSKI #3 simulates a 2 wk block with normal, or a 1 wk block with reduced turnover.

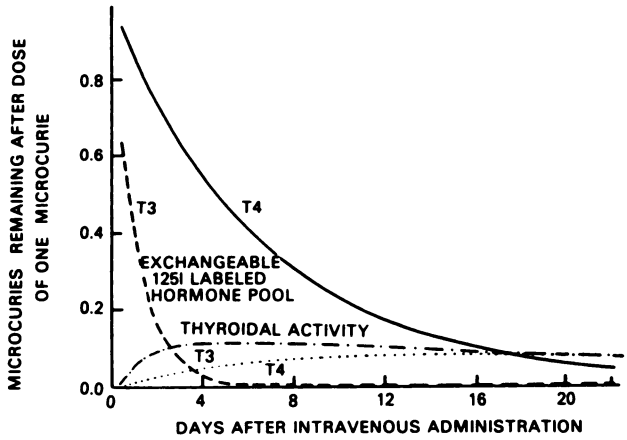

FIGURE 2
Time-activity curve for exchangeable pools of ^{125}I-T_4 and ^{125}I-T_3 and for thyroidal content of ^{125}I after administration of each

TABLE 2
Maximum Amounts of Radioiodinated Hormones in μc, Given 10, for 5 rad Limit

Item	No Block	SSKI #1	SSKI #2	SSKI #3
Radioiodinated T_4				
^{123}I	7,680	8,930*	—	—
^{124}I	25	40	100	329*
^{125}I	14	18	32	91
^{131}I	13	18	38	180
Radioiodinated T_3				
^{123}I	1,114	15,625	—	—
^{124}I	14	49	452	484†
^{125}	14	42	306	2,717†
^{131}I	8	28	232	479†

Note: The amount radioiodinated hormones that have been studied which can be administered within the limits of 5 rad to any organ under the various conditions of RAIU block studied. Except where indicated by footnote, the dose-limiting organ is the thyroid.

* Critical organ is the liver.

† Critical organ is the right colonic wall.

in the thyroid. On the other hand, by 16 days after administration of [^{125}I]T_4 or [^{125}I]T_3, the thyroidal ^{125}I level is the same.

Figure 3 demonstrates the effects of an iodine block on thyroidal radioiodine activity for the ^{131}I and ^{125}I labeled hormones, respectively. One can see from this figure that the impact of a single blocking dose of iodine (SSKI #1) is more dramatic for ^{131}I than for ^{125}I and for T_3 than for T_4. After [^{125}I]T_4 injection, by 3 wk, even a week of iodine block results in thyroidal ^{125}I levels higher than after [^{125}I]T_3 with a single blocking dose.

The unabsorbed portion of an oral administration of T_4* or T_3* primarily irradiates the GI tract and ovaries. Radiation absorbed dose after an oral administration of ^{123}I, ^{124}I, ^{125}I or ^{131}I, which is retained in the GI tract is, respectively, stomach wall, 0.33, 1.84, 0.16, and 1.06 rads/mc; small intestinal wall, 1.14, 5.38, 0.65, and 2.59; right colonic wall, 3.82, 22.46, 2.71, and 18.16; left colonic wall, 12.31, 67.16, 10.70, and 65.08; liver, 0.07, 0.41, 0.01, and 0.16; red bone marrow, 0.37, 1.08, 0.22, and 0.49; ovaries, 1.44, 5.51, 0.81, and 2.49; testes, 0.09, 0.54, 0.02, and 0.24; thyroid, 0.00, 0.01, 0.00, and 0.00; and total body, 0.19, 0.92, 0.10, and 0.49 rads/mc. To use these values in calculating absorbed radiation from an oral dose, it is necessary to project the fraction absorbed. The dose is then split, the unabsorbed fraction calculated from these figures and the absorbed fraction calculated in the same way as an intravenous dose. Absorption of these hormones is rapid after gastric emptying, so the error introduced by this approach, which assumes immediate absorption, is small.

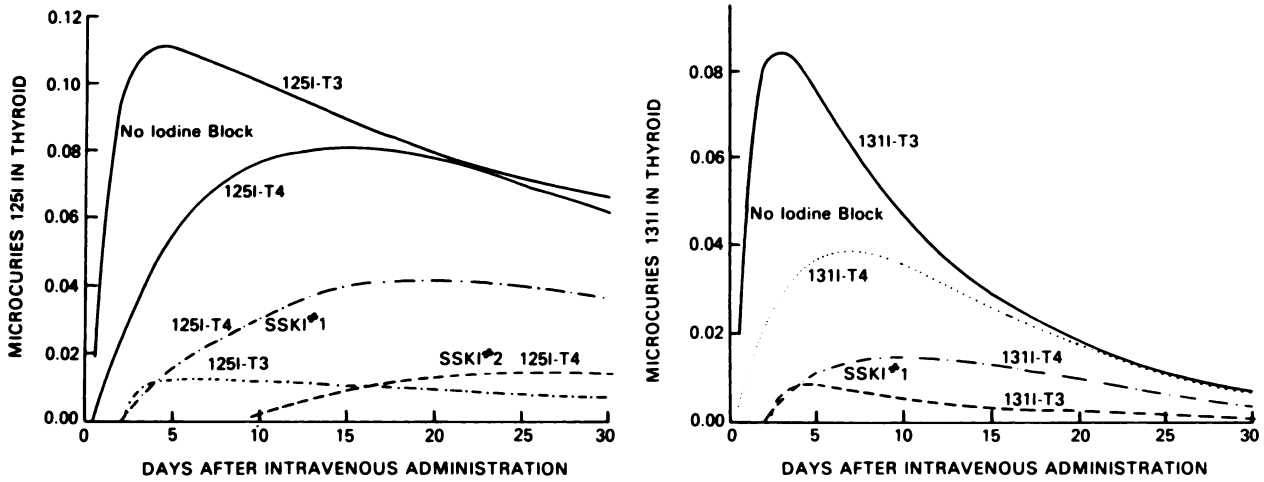

FIGURE 3
Effect of iodine block on thyroidal time-activity curve after T_4 and T_3 labeled with (left) ^{125}I and (right) ^{131}I

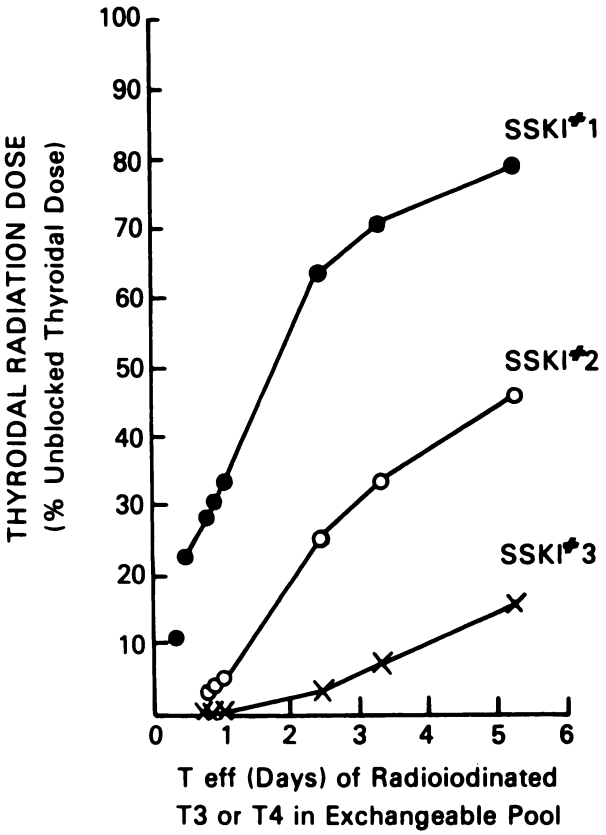

FIGURE 4
Fractional reduction in thyroidal radiation absorbed dose achieved with blocking conditions studied, as function of the effective half-life of exchangeable pool for labeled T_4 or T_3

DISCUSSION

Permissible limits for human administration of these radioiodinated hormones in a research setting are set at our institution based on occupational exposure limits. They are limited by a critical organ dose of 5 rad for a single administration or by an annual cumulative dose from repeat studies of 15 rad. Whole body dose, as well as that to the gonads, is limited to 3 rad, 5 rad cumulative. The maximum permissible single dose of the various radioiodinated hormones, with the dose-limiting organs, under the different circumstances simulated, are presented in Table 2. Obviously, if multiple radionuclides are administered, as with ^{123}I containing ^{124}I or ^{125}I, or in double or triple isotope kinetic studies, the amounts of each substance given must be adjusted to keep the total rad dose below permissible maxima.

While the shapes of the time-activity curves for the various T_4's and T_3's vary, it is possible to derive overall effective half-lives directly from the integrated values used in these calculations. Figure 4 shows that the overall T_{eff} of the circulating hormone pool, which is minimally affected by iodine blockade, is nevertheless closely related to the sensitivity of thyroidal radiation to the various degrees of iodine block studied.

Estimation of the total μc-hr figures from physiologic studies continues to be the aspect of radionuclide radiation dosimetry calculations most subject to fluctuation and inaccuracy. Often, physiologic parameters are expressed as multiexponential equations empirically derived to fit observed or simulated time-activity curves. This approach does not allow for changes in biologic activity such as that produced by iodine blockade. In addition, the coefficients of a multiexponential equation seldom have intuitive meaning to the clinician. Now that Consam and similar modeling techniques have become widely accessible, it is practical to work directly with, and to vary, the physiologic parameters of interest. Physical decay simply becomes an added model parameter, to be manipulated at will. This study is an example of such explorations, examining the impacts of variations in RAIU and of iodide turnover on radiation effects from the radioiodinated thyroid hormones. We are now applying the results to the design of upcoming human studies.

ACKNOWLEDGMENT

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