RATES OF I^{131}-LABELED THYROXINE METABOLISM IN EUTHYROID CHILDREN

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Studies of the requirements for thyroid hormone by infants and children suggest that they may be relatively higher than those of adults (1–3). Although the plasma concentration of thyroid hormone in newborn infants is appreciably higher than in adults, in children there appears to be no significant difference (4–9). The present study of thyroxine metabolism was designed to further define thyroid hormone metabolism in children.

MATERIAL AND METHODS

Seventeen children were included in this study; their ages varied between 3 and 9 years. All were institutionalized because of mental retardation[1] but showed no evidence of metabolic, endocrine or physical defects. They were all clinically and biochemically euthyroid, and maintained a height:age and osseous development corresponding to their chronological ages. Thyroxine labeled with radioiodine[2] was given intravenously. Beginning one day prior to injection, methimazole (Tapazole) in 10 mg doses every 8 hours was administered orally to each child for 10 days, to inhibit uptake of radioiodine by the thyroid. Serum protein-bound iodine (PBI), determined by the alkaline ash method of Barker, Humphrey and Soley (10), was estimated before and on the eighth day of the study. After the administration of radioactive thyroxine, heparinized venous blood samples were collected at 10 and 30 minutes at 1, 1.5, 2, 4, 8, 12 and 24 hours, and at daily intervals thereafter for 8 to 10 days. The heparinized plasma was separated promptly by centrifugation; 1 ml plasma samples were counted in a well-type scintillation counter in series with a standard of the same volume consisting of a suitable dilution of the injection material.

Urine and stool collections were made on two subjects. Aliquots of urine were counted in the same way as the plasma. The stools were collected in disposable tin cans, homogenized with water containing a few pellets of sodium hydroxide, and counted in series with a standard of equal volume over a wide well-type scintillation counter.

The radioactivity of each sample counted was expressed as a fraction of the injected dose.

RESULTS

The data were plotted on semilogarithmic coordinates as shown in Figure 1. A good fit of the data could be obtained with a minimum of three exponential components. There was a very fast initial component which was assumed to represent a mixing phase of the radioactive hormone during the first 2 hours after its injection. This component was therefore neglected in the analysis. The remaining two components —a relatively fast one followed by a slow component—suggested a two-compartment system, as shown in Figure 2. The half-life for radioactive thyroxine was calculated only for the slow component $\left(T_{\frac{1}{2}} = \frac{0.693}{\alpha_2}\right)$.

The method of Berman and Schoenfeld (11) was employed for the solution of the two-compartment system shown in Figure 2. Compartment 1 was considered to represent the plasma. The specific activity in the plasma (X_1) may be expressed as a sum of two exponentials:

$$X_1 = X_{11}e^{-\alpha_1 t} + X_{12}e^{-\alpha_2 t} \qquad [1a]$$

where X_{11} and X_{12} are the intercepts for the two components at time (t) = 0.

Normalized to $X_1 = 1$ at $t = 0$, Equation 1a can be rewritten as:

$$q_1 = A_{11}e^{-\alpha_1 t} + A_{12}e^{-\alpha_2 t} \qquad [1b]$$

where q_1 is the total radioactivity of the plasma (compartment 1) at any time t; $A_{11} + A_{12} = 1$.

The general solution of the turnover rates (λ's) of any two-compartment system may be given in terms of the constants of Equation 1b

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[1] The patients were selected from the D. C. Training School, Laurel, Md.

[2] Supplied by Abbott Laboratories, Oak Ridge, Tenn. Radioactive thyroxine was kept cold and away from light. It was tested for radiochemical purity by paper chromatography, and it was purified, when necessary, to 90 per cent purity or better.

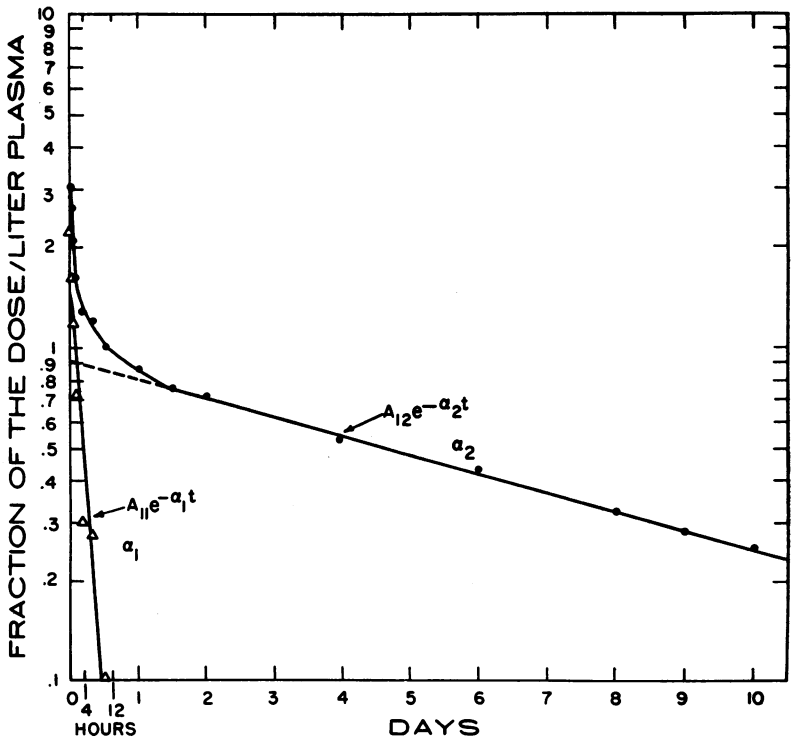

FIG. 1. SEMILOGARITHIMIC PLOT OF THE PLASMA DISAPPEARANCE CURVE FOR I^{131}-LABELED L-THYROXINE. α_1 and α_2 represent the exponential constants for the two components of the two-compartment system model.

as follows:

$$\lambda_{11} = \lambda_{01} + \lambda_{21} = A_{11}\alpha_1 + A_{12}\alpha_2 \quad [2a]$$

$$\lambda_{22} = \lambda_{02} + \lambda_{12} = A_{11}\alpha_2 + A_{12}\alpha_1 \quad [2b]$$

$$\lambda_{12} = \frac{A_{11}A_{12}}{A_{22}}(\alpha_1 - \alpha_2) \quad [2c]$$

$$\lambda_{21} = A_{22}(\alpha_1 - \alpha_2) \quad [2d]$$

$$\lambda_{01} = \lambda_{11} - A_{22}(\alpha_1 - \alpha_2) \quad [2e]$$

$$\lambda_{02} = \lambda_{22} - \lambda_{12} \quad [2f]$$

where A_{22} = the intercept for the radioactivity curve in compartment 2 which is unknown in this study; λ_{11} and λ_{22} = the total turnover rates from compartment 1 and compartment 2, respectively (Figure 2). To ensure that each of the λ's be positive, the range of A_{22} is limited by Equations 2a to 2f and must be as follows:

$$\frac{A_{11}A_{12}(\alpha_1 - \alpha_2)}{A_{11}\alpha_2 + A_{12}\alpha_1} \leqslant A_{22} \leqslant \frac{A_{11}\alpha_1 + A_{12}\alpha_2}{\alpha_1 - \alpha_2}. \quad [3]$$

Assuming that an amount Z of thyroxine per unit time enters the system through compartment 1, the volume of compartment 1 = (C_1) and the volume of compartment 2 = (C_2) may be obtained as follows:

$$C_1 = \left(\frac{A_{11}}{\alpha_1} + \frac{A_{12}}{\alpha_2}\right) Z \quad [4a]$$

$$C_2 = A_{22}\left(\frac{1}{\alpha_2} - \frac{1}{\alpha_1}\right) Z \quad [4b]$$

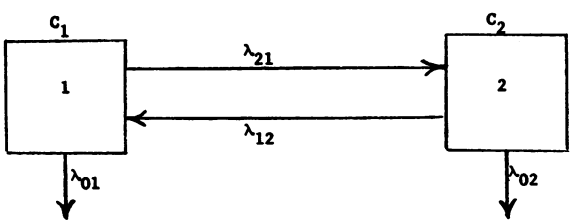

FIG. 2. A TWO-COMPARTMENT SYSTEM MODEL. C_1 = volume of compartment 1 and is equal to pool size of stable thyroxine with plasma as shown in Table I; C_2 = volume of compartment 2; λ_{01} and λ_{02} = the turnover rates from C_1 and C_2, respectively; λ_{21} and λ_{12} = the turnover rates from C_1 into C_2 and from C_2 into C_1, respectively; $\lambda_{11} = \lambda_{01} + \lambda_{21}$; $\lambda_{22} = \lambda_{02} + \lambda_{12}$.

from which

$$\frac{C_2 + C_1}{C_1} = 1 + \frac{A_{22}(\alpha_1 - \alpha_2)}{A_{11}\alpha_2 + A_{12}\alpha_1}$$

$$= 1 + \frac{\alpha_1 - \alpha_2}{\lambda_{22}} A_{22}. \quad [5]$$

Since the range of A_{22} is known from Equation 3, the range of $\frac{C_2 + C_1}{C_1}$ may thus be calculated.

The turnover rate of the system as a whole may be expressed as λ_{0T}:

$$\lambda_{0T} = \frac{\lambda_{01}C_1 + \lambda_{02}C_2}{C_1 + C_2} = \frac{\lambda_{01}}{\frac{C_1 + C_2}{C_1}} + \frac{\lambda_{02}}{\frac{C_1 + C_2}{C_2}}. \quad [6]$$

Again, using Equations 2, 3 and 5, the range of λ_{0T} may be calculated.

The values of all the λ's and the ratio $\frac{C_1 + C_2}{C_1}$ may not be uniquely determined without further assumptions (12). If one chooses to restrict the model of Figure 2 so that the degradation of thyroxine takes place in compartment 2 only, which presumably represents the extravascular space of thyroxine, λ_{01} equals 0; and Equations 2a and 2e yield

$$A_{22} = \frac{A_{11}\alpha_1 + A_{12}\alpha_2}{\alpha_1 - \alpha_2}. \quad [7]$$

This value of A_{22} permits the calculation of all the remaining λ's.

The volume of compartment 1 = (C_1) may be determined from the original data, since at t = 0,

$$(X_{11} + X_{12})C_1 = 1 \quad \text{or} \quad C_1 = \frac{1}{X_{11} + X_{12}}. \quad [8]$$

Assuming the plasma PBI is totally thyroxine, the effective extrathyroidal thyroxine (ETT_4) and the rate of degradation of thyroxine in micrograms per day (ρs/day) may be extimated:

$$ETT_4 = (C_1 + C_2) \cdot PBI \quad [9]$$

$$\rho s/day = (C_2) \cdot \lambda_{02} \cdot PBI \quad [10]$$

where ($C_1 + C_2$) = the effective extrathyroidal pool in liters; the PBI = micrograms per liter; and (C_2) = the volume of compartment 2 in liters.

In plotting the data on the urine and the stool, the rate of the appearance of the radioactivity in both was found to parallel that of its disappearance from the plasma. When expressed in terms of percentage of the dose, the radioactivity in the urine was about 4 per cent per 24 hours and that in the stool about 1 per cent per 24 hours of the remaining radioactivity in the body.

TABLE I

*Radioactive thyroxine metabolism in 17 children**

Subjects	Sex	Age		Weight	Surface area	PBI		Half-life	Turnover rate	Degradation rate	TVD	ETT_4	Plasma thyroxine
						Initial	8th day						
		yrs	*mos*	*kg*	m^2	*μg/%*		*days*	*% dose/day*	*μg/day*	*L*	*μg*	*μg*
L.A.	♂	5		17.5	0.7	5.9		4.9	13.7	24.2	2.986	177.1	55.1
J.A.	♂	5		15.5	0.6	6.2		4.3	15.5	16.8	1.745	108.9	39.4
E.D.	♂	3	11	15.8	0.6	5.9	6.6	5.8	11.7	15.6	2.133	133.7	40.4
T.L.E.	♂	4		15.0	0.6	5.2	6.2	4.7	14.3	14.0	1.711	97.4	34.1
R.J.	♂	3	5	15.0	0.5	6.7	5.6	4.4	15.0	25.6	3.152	195.4	46.5
L.B.	♀	5		16.2	0.6	7.1	7.4	5.4	12.5	19.9	2.167	156.9	53.4
R.G.	♀	4		14.8	0.6	7.1		4.6	14.4	21.2	2.079	147.5	49.9
D.M.	♂	6		18.2	0.7	5.2	6.2	3.9	16.8	27.8	2.953	165.3	58.0
K.M.	♂	6	6	17.8	0.7	5.7	6.5	5.5	12.8	19.3	2.567	158.7	54.0
W.T.	♂	3	9	14.2	0.6	7.0		5.1	13.2	23.7	2.531	179.7	55.4
W.T.	♂	3	11	14.5	0.6	7.1		5.1	13.4	13.8	1.488	102.9	31.6
R.K.	♂	8	9	16.9	0.7	5.1		5.9	12.3	15.8	2.721	139.0	60.3
M.L.	♂	8	7	16.7	0.7	6.9	5.7	5.3	10.5	19.2	2.881	182.9	51.9
D.W.	♂	3	4	12.9	0.5	5.2	6.2	4.5	18.7	20.0	1.891	106.8	33.7
S.L.	♀	4		13.6	0.6	7.3	6.6	4.2	16.0	21.5	1.913	134.2	51.6
L.B.	♂	5	5	15.8	0.6	4.4	4.7	5.1	13.1	23.7	3.964	181.0	36.8
D.B.	♂	3	7	11.4	0.5	5.1	4.9	5.5	12.3	12.5	2.024	101.6	32.7
Mean						6.06		4.95	13.89	19.68	2.406	145.2	46.16
SE						0.21		0.13	0.47	1.04	0.150	7.7	2.29

* PBI (initial, 8th day) indicates PBI values before and 8 days after Tapazole administration; TVD = effective total volume of distribution ($C_1 + C_2$) of thyroxine; ETT_4 = effective extrathyroidal thyroxine.

TABLE II

*Thyroxine metabolism in children as compared with reported values in adults**

	Child data		Adult mean	
	Range	Mean ± SE	Ref. 16 ± SE	Ref. 17
Half-life (days)	3.9–5.9	4.95 ± 0.13	6.7 ± 0.3	6.6
Turnover rate (% dose/day)	10.5–18.7	13.89 ± 0.47	10.5 ± 0.4	10.56
TVD (L)	1.488–3.964	2.406 ± 0.156	8.890 ± 0.624	9.400
(per m^2)	2.480–6.607	3.951 ± 0.252	4.559 ± 0.191	
(per kg)	0.103–0.210	0.156 ± 0.008	0.116 ± 0.005	
ETT_4 (μg)	101.6–195.4	145.2 ± 7.7	548 ± 38	508
(per m^2)	162.3–390.8	238.4 ± 13.1	281.8 ± 16	
(per kg)	6.5–13.0	8.9 ± 0.7	7.16 ± 0.4	
Degradation rate (μg/day)	12.5–27.8	19.68 ± 1.04	57.0 ± 4	53.6
(μg/m^2)	22.6–42.7	32.0 ± 1.61	29.4 ± 1.6	
(μg/kg)	0.9–1.7	1.29 ± 0.06	0.75 ± 0.04	

* See references 16 and 17; see footnote to Table I for abbreviations.

The radioactivity in the urine was assumed to represent the excretion of inorganic I^{131} which was liberated from the peripheral degradation of I^{131}-labeled thyroxine (13, 14). Fecal radioactivity, on the other hand, has been shown to be largely organic I^{131} (14), representing the end-product of the hepatic degradation of thyroxine [its conjugation and its hepatointestinal cycle (15)].

DISCUSSION

In general, the calculations described above give values for thyroxine turnover rate, half-time, degradation rate and extrathyroidal thyroxine pool (TVD) about 5 to 10 per cent higher than when the method of Sterling and Chodos (16) is used. The results of the present studies are listed in Table I, and in Table II they are compared with similar values obtained in adults by the Sterling-Chodos method and by others (16, 17).

Plasma thyroxine, when estimated empirically according to an estimated plasma volume for this age group of patients (18, 19), coincided with the calculated value of thyroxine in compartment 1. The ETT_4 or effective pool of thyroxine, on the other hand, seems to be about 30 per cent less than that of the extracellular fluid volume for this age group estimated by Edelman and colleagues (20). This apparent decrease in ETT_4 is possibly effected by the decreased thyroxine-binding capacity in the extracellular fluid as compared with that in the plasma (21), which occurs in a ratio of 1:2.

In Table II, the child seems to use thyroxine at a faster rate than does the adult, as suggested by the shortened half-life. His extrathyroidal thyroxine pool and thyroxine daily requirements are, however, about one-fourth and one-third those of the adult, respectively. In order to estimate the significance of this increase in the turnover rate of thyroxine in the child, the degradation rate and the extrathyroidal pool for thyroxine are calculated in terms of micrograms per square meter of surface area and micrograms per kilogram of body weight. When the surface area parameter is considered, the degradation rate of thyroxine in the child is not significantly larger than that in the adult. The effective extrathyroidal pool, however, is somewhat smaller in the child per square meter than in the adult. It would thus appear that the increase in thyroxine turnover in the child is more a function of the difference in body configuration than an actual increase in thyroxine utilization. When the body weight parameter is used, the conclusion favors an actual increase in thyroxine degradation by the child. It is quite possible that both factors play a role in the metabolism of thyroxine by the child, namely, a decreased pool and an increased turnover of thyroxine.

The children studied demonstrated no significant effect of age on either half-life or degradation rate for thyroxine. Nonetheless, since infants or adolescents were not included in this study, it is difficult to predict the variation that may exist among these three age groups, and in comparison with the adult.

SUMMARY

The metabolism of labeled thyroxine was studied in 17 euthyroid children between the ages of 3 and 9 years. Compared with adults, a more rapid turnover rate (13.9 per cent per day) was found. The amount of thyroxine degraded per day in micrograms per square meter of body surface was similar for children and adults although, per kilogram of body weight, children utilized more than did the adults.

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