Upsala J Med Sci 81: 147–149, 1976

Factors Influencing the Early Plasma Disappearance Rate and Liver Uptake of Thyroxine

G. JÄRNEROT, S. C. TRUELOVE, G. T. WARNER, B. KÅGEDAL and H. von SCHENCK

From the Nuffield Department of Clinical Medicine, the Radcliffe Infirmary, Oxford, England, and the Departments of Clinical Chemistry, Linköping University, Medical School, Linköping, and Malmö General Hospital, Malmö, Sweden

ABSTRACT

The early disappearance from plasma (T 1/2) of i.v. administered thyroxine (T_4) labelled with ^{131}I was studied in order to find a simple biochemical parameter with which it could be correlated in health and disease. The radioactivity of the liver was also measured by surface counting to determine the time for the peak liver count rate. The T 1/2 for the ^{131}I–T_4 showed a correlation of borderline significance with T_4 in plasma but a good correlation was found with T_4-binding globulin (TBG) in plasma and an even better with the T_3-test. The T_3-test showed a significant correlation with TBG but when the T_4-binding capacity of prealbumin (TBPA) was taken into account the correlation was even better indicating that the result of the T_3-test was not only dependent on the TBG concentration in plasma but also on the TBPA.

The T 1/2 correlated best with the time for the liver peak count rate. The study supports the hypothesis that in the early distribution phase of T_4, the free binding sites extracellularly and the available intracellular binding locations compete for T_4 until a state of equilibrium is reached.

The early disappearance rate of thyroxine (T_4) after i.v. injection has been studied in healthy volunteers, in patients with functional thyroid disorders or liver disease and in subjects with abnormal concentration of thyroxine-binding globulin (TBG) (3, 7, 8, 10, 12). The aim of the present study was to find a simple biochemical parameter which could be correlated to the early disappearance rate of T_4 in health and disease and to study the intracellular uptake of T_4 during its early distribution phase as reflected by the time for the peak count rate over the liver. In order to fulfil the criteria of "health and disease" a heterogenous material was studied.

MATERIAL AND METHODS

The material consisted of six healthy volunteers, two of whom were taking the contraceptive pill and five patients with ulcerative colitis (UC) or Crohn's disease. One of the patients was taking the contraceptive pill and three others were being treated with corticosteroids.

Before the study began uptake of radioiodide by the thyroid was blocked by potassium iodide and T_4 labelled with ^{131}I was prepared as described earlier (5). The ^{131}I–T_4 was injected i.v. in a measured amount of 10 μCi. Blood was drawn every ten minutes between 25 and 75 minutes after the injection of ^{131}I–T_4. After separation the plasma was counted in a sodium iodide well counter. The plasma proteins were then precipitated with 10% trichloroacetic acid and the precipitate and the supernatant were counted to evaluate the amount of ^{131}I existing as free iodide. The half-life (T 1/2) for the early disappearance of T_4 was calculated from the regression line by plotting the plasma counts between 25 and 75 minutes semilogarithmically.

Five minutes after the injection of ^{131}I–T_4 and at the same time intervals as the blood was drawn, the radioactivity over the point of maximum liver dullness was measured in order to decide the time for the peak count rate. The liver counting continued regularly for a total period of 180 min.

The concentration of T_4–I in serum was determined using a method for competitive protein-binding (11) modified by the use of purified TBG as the binding protein. The ^{125}I-triiodothyronine uptake test (T_3-test) was performed using Sephadex as the adsorbent (9). The maximum thyroxine-binding capacities of TBG and thyroxine-binding prealbumin (TBPA) were measured by agar gel electrophoresis at pH 8.6 with trismaleate as buffer (2).

RESULTS

The results of the T 1/2 for the early ^{131}T–T_4 disappearance from plasma, the T_3-test and of the concentrations of T_4–I as well as the maximum T_4-binding capacities of TBG and TBPA are shown in Table I together with the time for the peak liver count rate and some clinical details of the subjects studied.

The radioactivity in plasma was well above the

Table I. *Results for the individual subjects in the study*

Sex	Clinical details	T 1/2 for ^{131}I–T_4 (min)	Time for peak liver count rate (min)	T_4–I/s (2.9–6.3 μg/100 ml)	T_3-test (%)	TBG/s (15–25 μg T_4/ 100 ml)	TBPA/s (140–220 μg T_4/ 100 ml)	TBG + TBPA/60
M	Volunteer	96	65	4.8	107	20	145	22.4
M	Volunteer	93	95	3.1	88	19	145	21.4
F	Volunteer	98	90	5.5	107	22	116	23.9
F	Volunteer	108	90	3.4	127	13	152	15.5
F[a]	Volunteer	132	110	4.3	76	22	100	23.7
F[a]	Volunteer	149	180	5.7	90	23	120	25.0
M[b]	Severe UC	64	65	2.2	154	15	42	15.7
M[b]	Severe UC	67	65	3.6	156	18	52	18.9
F[b]	Distal UC	136	170	2.9	99	25	137	27.3
F	Crohn's disease of the small bowel	88	65	4.7	94	26	80	27.3
F[b]	Crohn's disease of the small bowel	166	175	6.7	57	39	63	40.1

[a] Subjects on the contraceptive pill.
[b] Patients treated with corticosteroids.

background activity and straight lines were produced when the counts were plotted semilogarithmically. No difference was noted in the number of counts before and after precipitation with trichloroacetic acid, indicating that a negligible amount of the ^{131}I existed as free iodide.

In the four healthy volunteers who were not taking the contraceptive pill the T 1/2 of the ^{131}I–T_4 disappearance was 93–108 min and considerably longer (132–166 min) in the three women who were taking the contraceptive pill. The T 1/2 was about 30 minutes shorter in the two patients with severe UC than in the drug-free volunteers.

Table II shows that the T 1/2 for ^{131}I–T_4 showed a positive correlation with the T_4–I in plasma but of borderline significance (p=0.05). TBPA in plasma did not significantly correlate with the T 1/2 which TBG in plasma did ($p<0.02$). An even better correlation was found between the T 1/2 and the T_3-test ($p<0.01$). However, the very best correlation for the T 1/2 was found with the time for the peak liver count rate ($p<0.001$).

The T_3-test showed a significant negative correlation with TBG in plasma ($r=-0.76$, $p<0.01$) but it correlated even better with the combined results of TBG and TBPA ($r=-0.80$, $p<0.01$).

DISCUSSION

Earlier studies have shown a correlation between the concentration of T_4 or TBG in plasma and the early disappearance rate of T_4 (12). This was confirmed in the present study but we found that the T_3-test correlated better than TBG or T_4 with the T

Table II. *The correlation between the T 1/2 and different biochemical parameters and the time for the peak liver count rate as well as between the T_3-test and the T_4-binding proteins*

Correlated parameters	Formula for the regression line		Statistical significance
T 1/2–T_4–I/s	$y=14.5x+47.0$	0.60	$p=0.05$
T 1/2–TBPA/s	$y=0.2x+87.8$	0.24	N.S.
T 1/2–TBG/s	$y=3.3x+35.9$	0.69	$p<0.02$
T 1/2–T_3-test	$y=200-0.88x$	−0.80	$p<0.01$
T 1/2–time for the peak liver count rate	$y=0.64x+40.0$	0.91	$p<0.001$
T_3-test–TBG/s	$y=178.8-3.4x$	−0.76	$p<0.01$
T_3-test–$\left(\text{TBG/s}+\frac{\text{TBPA/s}}{60}\right)$	$y=190.5-3.60x$	−0.80	$p<0.01$

1/2. The T_3-test result reflects the number of free binding sites on the thyreoid hormone binding proteins, mainly on the TBG but also on the other thyroid hormone binding proteins (4) which was confirmed in the present study. The results presented in this study showed that the early disappearance of ^{131}I–T_4 from plasma was determined by the number of free binding sites on these proteins as reflected by the T_3-test.

After i.v. injection of T_4 a large proportion of the administered dose is rapidly distributed intracellularly. In particular the liver accumulates a considerable part of the T_4 in the early distribution phase (1, 3, 8) provided that it is not grossly diseased, in which case the uptake of T_4 is reduced (10) and the T 1/2 for the early disappearance from plasma is prolonged (7). The present study was not designed to estimate the proportional liver uptake of the administered dose of ^{131}I–T_4 but an earlier study showed that the liver uptake is 70–80% of the intracellular uptake during the early distribution phase (10). Why liver accumulates such a high proportion of T_4 is not known. Liver biopsies have not shown more T_4-binding proteins in liver tissue than could be expected from its plasma content (10). Dowling et al. (3) found a strong correlation between the hepatic T_4 uptake and the T_4 rate of disappearance from the plasma which was confirmed in the present study.

Diphenylhydantoin which competes with T_4 for the binding sites on TBG (13) increases the liver uptake of T_4 and its faecal excretion (6, 10). Conversely estrogens, which increase the TBG concentration in plasma, decrease the early disappearance of T_4 from plasma and also the liver uptake (8, 12) while the conditions are reversed in TBG-deficiency (3, 10). These findings strongly suggest that in the early distribution phase of T_4, the free binding sites extracellularly and the available intracellular binding locations compete for T_4 until a state of equilibrium is reached. The results presented here, which showed that the early disappearance rate varied with the T_3-test result and also with the time for the peak count rate over the liver support such a hypothesis.

REFERENCES

1. Cavalieri R. R., Searle G. L., Castle J. N. & Dickard R: The kinetics of distribution between plasma and liver of ^{131}I-labeled l-thyroxine in man: Observations of subjects with normal and decreased serum thyroxine-binding globulin. J Clin Invest *45:* 939, 1966.
2. DiGiulio W, Michalak Z., Weinhold P. A., Hamilton J. R. & Thoma G. J.: Use of agar gel electrophoresis and autoradiography to measure thyroxine-binding protein capacities. J Lab Clin Med *64:* 349, 1964.
3. Dowling J. T., Appleton W. G. & Musa B. U.: Direct measurement of hepatic thyroxine flux in normal man. J Clin Endocr *28:* 1053, 1968.
4. Järnerot G.: *In* The Thyroid in Ulcerative Colitis and Crohn's Disease, pp. 33–34. Linköping University Medical Dissertations No. 26, 1974.
5. Järnerot G., Truelove S. C. & Warner G. T.: The thyroid in ulcerative colitis and Crohn's disease. III. The Daily fractional turnover. Acta Med Scand *197:* 89, 1975.
6. Larsen P. R., Atkinson A. J., Jr, Wellman H. N. & Goldsmith R. E.: The effect of diphenylhydantoin on thyroxine metabolism in man. J Clin Invest *49:* 1266, 1970.
7. Lennon E. J., Engbring N. H. & Engström W. W.: Studies of the rate of disappearance of labeled thyroxine from the intravascular compartment. J Clin Invest *40:* 996, 1961.
8. Musa B. U., Kumar R. S. & Dowling J. T.: Role of thyroxine-binding globulin in the early distribution of thyroxine and triiodothyronine test. J Clin Endocr *29:* 667, 1969.
9. Nosslin, B.: A simplified technique for the triiodothyronine test (T_3-test) with Sephadex. Scand J Clin Lab Invest Suppl *86:* 177, 1965.
10. Oppenheimer J. H., Bernstein G. & Hasen J: Estimation of rapidly exchangeable cellular thyroxine from the plasma disappearance curves of simultaneously administered thyroxine–^{131}I and albumin–^{125}I. J. Clin Endocr *46:* 762, 1967.
11. Seligson H. & Seligson D.: Measurement of thyroxine by competitive protein binding. Clin Chim Acta *38:* 199, 1972.
12. Websters B. R., Britton A., Volpé R. & Ezrin C.: Further studies on the rate of disappearance of labelled thyroxine from the intravascular compartment of man, with reference to the role of thyroxine binding proteins. Acta Endocr (Kbh) *55:* 497, 1967.
13. Wolff J., Standaert M. E. & Rall J. E.: Thyroxine displacement from serum-proteins and depression of serum proteinbound iodine by certain drugs. J Clin Invest *40:* 1373, 1961.

Received February 24, 1976

Address for reprints:

Gunnar Järnerot, M.D.
Department of Medicine
Region hospital
S-701 85 Örebro
Sweden