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Thyroid Adaptation to Chronic Tetraglycine Hydroperiodide Water Purification Tablet Use*

HOMER J. LEMAR, WILLIAM J. GEORGITIS, AND MICHAEL T. MCDERMOTT

Endocrinology Service, Department of Medicine, Madigan Army Medical, Center (H.J.L.), Tacoma, Washington 98431; and the Endocrine Service, Department of Medicine, Fitzsimons Army Medical Center (W.J.G., M.T.M.), Aurora, Colorado 80045

ABSTRACT

Tetraglycine hydroperiodide tablets purify water by liberating 8 mg free iodine/tablet. The effects of ingesting four tablets daily for 3 months on thyroid size, function, and radioactive iodine uptake were studied prospectively in eight healthy volunteers. Serum inorganic iodide increased from 2.7 to approximately 100 μg/dL. Urinary iodide excretion rose 150-fold from a pretreatment mean of 0.276 to 40 mg/day. Radioactive iodine uptake was less than 2% after 7 days and remained below 2% in all subjects at 90 days. Mean serum T_4 and T_3 declined after 7 days. T_4 remained below baseline, whereas T_3 had recovered by the end of the treatment period. Serum TSH and the TSH response to TRH rose significantly after 7 days and remained elevated at 3 months. The average thyroid volume, determined by ultrasound, increased by 37%. Neither hyperthyroidism nor hypothyroidism was observed. The mean thyroid volume in seven subjects available for repeat determinations an average of 7.1 months after the study was not different from the baseline value. In normal subjects, a reversible TSH-dependent thyroid enlargement occurs in response to the iodine load from daily use of tetraglycine hydroperiodide water purification tablets. (*J Clin Endocrinol Metab* **80:** 220–223, 1995)

TETRAGLYCINE hydroperiodide (TGH) tablets, containing 20 mg of the germicidal ingredient globaline, are marketed for the purpose of purifying water. Globaline, $C_{16}H_{42}I_7N_8O_{16}$, is an iodine-rich compound with a solubility in water of approximately 380 g/L (1). Each tablet effectively disinfects 1 quart clear water or 0.5 quart tainted water by releasing approximately 8 mg free iodine. Consumption of water purified by this method delivers a daily iodine intake in amounts known to alter thyroid function in man (2–9).

Excessive iodide ingestion in the range of 1–150 mg/day by iodine-sufficient humans results in decreases in T_4 and T_3 levels of approximately 10–15% (2–6). This is accompanied by a 10-fold rise in serum TSH. Iodine loads from TGH have been shown to cause similar changes (7).

Thyroid volume and serum thyroglobulin levels were recently shown to increase during ingestion of an agent delivering 27 mg iodide/day over 4 weeks (8). The present investigation studied the effects of consuming the free iodine generated from dissolved TGH water purification tablets on thyroid size, thyroid radioiodine uptake, serum thyroid hormone levels, and basal and TRH-stimulated TSH levels over 12 weeks. This study confirms the occurrence of thyroid enlargement in response to iodide excess, with an extended period of observation during which no sign of escape from the dampening effect of iodide excess on thyroid function was detected.

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Address all correspondence and requests for reprints to: Homer J. LeMar, Jr., M.D., L.T.C., M.C., Endocrinology Service, Department of Medicine, Madigan Army Medical Center, Tacoma, Washington 98431–5000.

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Materials and Methods

Study subjects and study design

Eight healthy Caucasian volunteers (seven men and one woman), ranging in age from 35–47 yr, participated in this prospective study. All subjects were euthyroid, as assessed by physical examination, serum levels of thyroid hormones, and TSH. Thyroid antimicrosomal antibody titers were undetectable in every participant. None had any history of thyroid disease, chronic medical disorders, use of medications known to affect thyroid function, or reactions to iodine. Furthermore, all of the subjects ate foods consistent with a typical American diet.

All subjects provided written consent upon entering this study, which was approved by the institutional research committee. The protocol adhered to the policies for protection of human subjects, as prescribed in 40 CFR 46 in accordance with AR 40–38.

All subjects had the following initial evaluations. Blood was drawn for the determination of basal serum iodine, T_4, T_3, and TSH measurements. Another sample was obtained 20 min after an iv injection of TRH for the measurement of stimulated TSH (TSH-20). A 24-h urine sample was collected for measurement of urinary iodine. The 24-h radioactive iodine uptake (RAIU) was recorded after a 1-μCi dose of ^{131}I, with 10-min counting times. Thyroid volume was determined in the recumbent position by ultrasound.

After the initial measurements, the subjects were instructed to consume the iodine released by four water purification tablets dissolved in water or juice every day for 90 days. Serum iodine, T_4, T_3, TSH, and TSH-20 and urinary iodine measurements were repeated on days 7, 28, and 90. RAIU was remeasured on days 7 and 90, and thyroid volume was reassessed on days 35 and 90.

Laboratory methods

Serum T_4 was assayed using the T_4 Plus TDX system (Abbott Diagnostics, North Chicago, IL), a fluorescent polarization immunoassay with an intraassay coefficient of variation (CV) of 4.5%. Serum T_3 was measured by Autopack T_3 RIA (ICN, Horsham, PA), with an intraassay

CV of 4.7%. Serum thyroglobulin levels were assayed employing the Kalibre thyroglobulin RIA kit (Kronus, San Clemente, CA), with a sensitivity of 1 ng/mL. TSH was measured by the IMX ultrasensitive human TSH assay based on the microparticle enzyme immunoassay technology (Abbott Laboratories, Abbott Park, IL), with an intraassay CV of 3.3–5.2%. Urine and serum total protein-bound and inorganic iodines were assayed by autoanalyzer methodology at SmithKline Beecham (Van Nuys, CA). TGH tablets (Van Ben Industries, Clinton, MA) were provided by the U.S. Army Quartermaster Supply.

Radioiodine thyroid uptake

Twenty-four-hour RAIU determinations were performed using 1 μCi radioiodine (^{131}I). After calibration with a 1-μCi ^{131}I standard, thyroid counts were performed with an uptake probe placed 6.5 cm from the gland. One microcurie of ^{131}I was then administered to each subject by mouth. Twenty-four hours later, counts accumulated in 10 min were obtained over the thyroid and one thigh to assess background activity. The 24-h RAIU was calculated by the formula: % uptake = (average neck cpm − background cpm)/(standard cpm × 100). The probe was calibrated daily using a 339- to 389-kiloelectronvolt window. Before dosing for the 7-day 24-h RAIU, a residual background count was obtained. After correction for decay, this residual count was used to calculate the 7-day 24-h RAIU.

Thyroid volume determinations

Thyroid volume was determined by ultrasound, as described by Rasmussen (10), using a Picker Echoview System model 80L-DI ultrasound machine with a Rohe 7.5-megahertz/6-mm 2OM focus transducer. Briefly, longitudinal images were recorded to determine right and left lobe lengths. Serial transverse images were then made through each lobe at 0.5- to 1-cm intervals based on length. Paper tracings of images recorded on radiographic film were digitized, and volumes were calculated using Sigma Scan and Sigma Plot computer software programs (Jandel Scientific, San Rafael, CA). Measurement accuracy was verified with a rubber thyroid phantom determined to have a volume of 18 mL by water displacement. The precision of thyroid volume determined by this method was assessed in five study participants, each examined on five separate occasions before the treatment period. Coefficients of variation for these thyroid volume measurements ranged from 3.6–13.2%. The greatest volume for each of these five subjects was subsequently used as the pretreatment volume for that individual.

Statistical analysis

Results are expressed as mean ± SE, with a level of $P < 0.05$ considered statistically significant. Data were analyzed by analysis of variance, followed by Student-Newman-Keuls multiple comparisons tests.

Results

Serum inorganic, protein-bound, and urinary iodines

Baseline mean serum inorganic and urinary iodine levels were 2.7 μg/dL and 276 μg/24 h, respectively (Table 1). Both serum and urinary iodine had increased dramatically when retested after 1 week. Comparable levels were found on days 28 and 90.

Radioiodine thyroid uptake

Twenty-four-hour RAIU tests, performed before and after 7 and 90 days of treatment with four TGH water purification tablets daily, are shown in Fig. 1. Pretreatment baseline uptake ranged from 8–26% (mean ± SE, 16 ± 3.0). After 1 week, radioiodine uptake ranged from 0–2.3% (mean, 1.1 ± 0.3; $P < 0.001$) and remained low at 90 days (mean, 0.5 ± 0.2; $P < 0.001$) compared to baseline.

Serum thyroid hormones

Results for T_4 and T_3 are summarized in Table 2. The mean serum T_4 concentration fell slightly on day 7 and remained below the pretreatment value on days 28 and 90. The mean serum T_3 concentration was also lower than the initial value on day 7, but averaged above baseline on days 28 and 90. None of these changes was statistically significant.

Thyroid volume and TSH

Serum TSH and TSH-20 levels rose significantly by day 7 and remained elevated on days 28 and 90 (Table 2). Thyroid volume increased significantly by day 35 and slightly more by day 90 (Fig. 2). The mean increase in thyroid volume relative to baseline was 37%. The highest unstimulated serum TSH level recorded was 6.12 μU/mL, a more than 3-fold increase over that subject's pretreatment value. This subject also had the greatest change in thyroid volume, with a 1.8-fold increase. Changes in thyroid volume and unstimulated TSH levels from baseline were not significantly correlated ($r = 0.24$; $P = 0.56$). For seven subjects available for repeat determinations at an average of 7.1 months (range, 0.5–16.1) after the experimental period, mean thyroid volume was not different from the baseline value.

Daily ingestion of dissolved water purification tablets was well tolerated by all participants. No subject developed clinical features of hyperthyroidism, hypothyroidism, or symptomatic thyroid enlargement. During the iodine exposure, TSH persistently remained above initial values in all subjects, with one exception. After 3 months, TSH had fallen below this male subject's pretreatment value, but still was in the middle of the established normal range for TSH.

TABLE 1. Serum and urinary iodide determinations before and during tetraglycine water purification tablet use

	Before treatment	During treatment		
		Day 7	Day 28	Day 90
Serum				
I (μg/dL)	2.7 ± 1.0	93 ± 24[a]	102 ± 23[a]	101 ± 21[a]
PBI (μg/dL)	4.8 ± 0.5	32.0 ± 5.2[a]	29.8 ± 4.2[a]	27.7 ± 1.3[a]
Urine				
I (mg/day)	0.276 ± 0.061	37.2 ± 4.4[a]	42.5 ± 6.5[a]	35.0 ± 4.4[a]

Data shown are the mean ± SE (n = 8). Comparisons were made by analysis of variance and Student-Newman-Keuls test.
[a] $P < 0.001$.

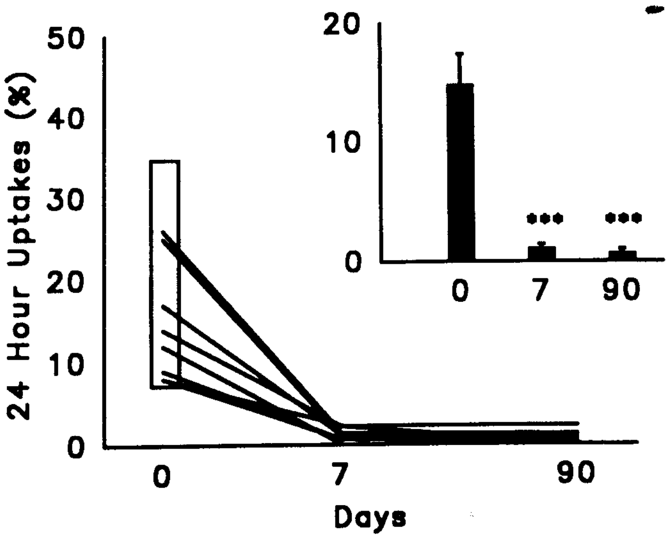

FIG. 1. Individual 24-h radioactive iodine uptake before and during TGH water purification tablet ingestion. The normal range of uptake is indicated by the *open rectangle*. RAIU decreased markedly at 7 days and remained low at 90 days. The mean + SEM are displayed in the *inset*. ***, $P < 0.001$.

Discussion

As demonstrated in the rat, iodide excess changes its own metabolism by the thyroid in one of four ways (11). Low doses cause proportionate increases in iodine incorporation into thyroid hormone while failing to alter the uptake of iodide by the thyroid. Moderate iodide excess decreases the percentage of available iodine taken up by the gland, but the resulting abundance of intrathyroidal iodine still leads to increased absolute rates of organification and hormone synthesis. Large doses of iodide initiate the Wolf-Chaikoff effect, with a diminished absolute rate of organification. Finally, with very large doses, the thyroid is believed to adapt to the surfeit of iodide by down-regulation of its iodide-transporting activity. Human thyroid gland function remains stable over a wide span of iodide intakes ranging from 50 μg to several milligrams per day (12). Goiter formation associated with iodine excess is rare in the absence of underlying thyroid defects (13, 14). This has been interpreted as an indication of the thyroid's ability to escape from the inhibitory effects of iodide (12). These thyroid adaptations to iodide excess represent autoregulation of iodine metabolism by the thyroid gland and appear to be independent of TSH (12).

The results of this study are consistent with those of prior studies using a variety of iodine preparations, doses, and treatment durations (2–9). Short term exposures to iodine excess lasting up to 2 weeks have shown a decline in serum T_4 accompanied by a rise in TSH (2–7). Longer treatment periods of 4–11 weeks demonstrate that these alterations persist (2, 8, 9).

Recently, thyroid enlargement was demonstrated by a study using 27 mg iodide/day from a licorice lecithin-bound iodine preparation (8). Thyroid volume increased by 16% after 4 weeks. This new observation is confirmed in the present study, in which a dose estimated to deliver 32 mg iodide/day induced changes remarkably similar in magnitude. In our study, the mean thyroid volume was 31% greater at 5 weeks than that before treatment and 37% greater at 12 weeks. In both investigations, the increase in thyroid volume was reversible. Declines in serum T_4 and elevations in serum TSH were very similar as well. Although not statistically significant by multiple comparison testing methods, the mean T_4 level fell and stayed lower than the preexposure level, whereas the mean T_3 level fell initially and then recovered.

The present study provides novel information about human thyroid gland adaptation to iodine excess in several respects. The elevation in TSH was shown to persist beyond 4 weeks and was maintained at 12 weeks. The amplified TSH response to TRH, reflecting releasable TSH

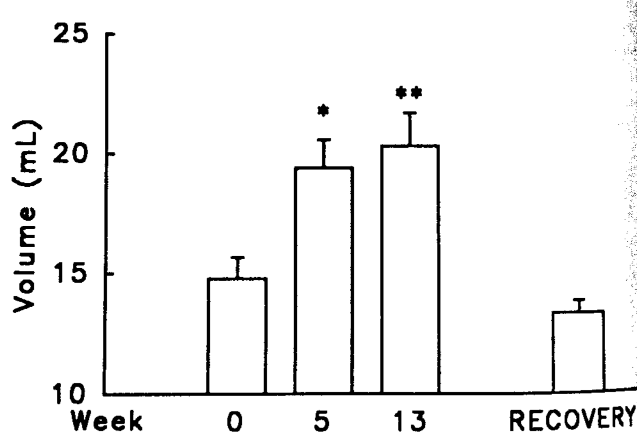

FIG. 2. Thyroid volumes before, during, and after TGH water purification tablet ingestion. Thyroid volume increased significantly after 5 weeks (day 35) of TGH ingestion and enlarged slightly more after 13 weeks (day 90). Thyroid volumes had returned to pretreatment values when remeasured at variable time intervals in seven subjects (mean, 7.1 months; range, 0.5–16.1 months). Shown are the mean + SEM. *, $P < 0.05$; **, $P < 0.01$.

TABLE 2. Effect of TGH treatment

	Before treatment	During treatment		
		Day 7	Day 28	Day 90
TSH (mU/L)	1.69 ± 0.09	2.80 ± 0.32[a]	3.30 ± 0.33[a]	2.98 ± 0.50[a]
TSH-20	9.90 ± 0.77	14.94 ± 2.41[a]	18.84 ± 1.72[b]	16.33 ± 1.69[a]
T_4 (nmol/L)	83.2 ± 2.9	77.6 ± 4.1	77.6 ± 3.8	78.9 ± 3.3
T_3 (nmol/L)	2.15 ± 0.12	1.97 ± 0.09	2.39 ± 0.15	2.29 ± 0.10
Tg (ng/mL)	13.9 ± 5.6	22.2 ± 9.3	31.4 ± 15.7[a]	23.3 ± 11.3

Data shown are the mean ± SE (n = 8). Tg, Serum thyroglobulin. Comparisons were made by analysis of variance and Student-Newman-Keuls test.

[a] $P < 0.05$.

[b] $P < 0.01$.

produced by the pituitary, was also demonstrated to last over the entire treatment period.

Based on animal (15–17) and human hemithyroidectomy models (18), could one interpret these adaptive changes to prolonged iodine excess in the following way? Iodine excess impairs the proteolysis of engulfed colloid in the follicular cell and dampens the release of T_4 from the gland. Sensing a decline in serum T_4 and T_3, the pituitary augments the release of TSH, attempting to restore circulating T_4. Under the influence of the effects of both prolonged iodine surplus and TSH stimulation, the thyroid gland manufactures and stores abundant amounts of colloid forming macrofollicles (15). Gradually, the thyroid enlarges; yet, this form of thyroid enlargement is capable of rapid reversal, because it represents hypertrophy, not hyperplasia (19).

This hypothesis incorporates an additional adaptive mechanism to iodine excess in the human, which is extrathyroidal and mediated by adjustments in the pituitary-thyroid axis. During prolonged iodide excess, the axis eventually may achieve a new steady state where the thyroid, after sufficient hypertrophy, compensates for the dampening effect of iodide excess on proteolysis and releases adequate quantities of thyroid hormone to allow TSH to decline to preexposure levels. Although serum thyroglobulin levels remained higher after 3 months than before exposure to iodine, there was a trend to fall toward baseline in all subjects. Therefore, in this model, assuming no change in the composition of thyroglobulin regarding thyroid hormone moieties, the elevated thyroglobulin levels may resolve during prolonged exposure to high doses of iodide as TSH returns to the pretreatment set-point. Further studies of longer durations using high to very high doses of daily iodine, serial measurements of thyroid volume, TSH by sensitive assays, and serum thyroglobulin should clarify further the human thyroid's adaptive mechanisms to chronic iodide excess.

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References

1. **Budavari S, ed.** 1989 The Merck index, 11th ed. Rahway: Merck; 1451.
2. **Vagenakis AG, Downs P, Braverman LE, Burger A, Ingbar SH.** 1973 Control of thyroid hormone secretion in normal subjects receiving iodides. J Clin Invest. 52:528–532.
3. **Vagenakis AG, Rapoport B, Azizi F, et al.** 1974 Hyperresponse to thyrotropin-releasing hormone accompanying small decreases in serum thyroid hormone concentrations. J Clin Invest. 54:913–918.
4. **Saberi S, Utiger RD.** 1975 Augmentation of thyrotropin responses to thyrotropin-releasing hormone following small decreases in serum thyroid hormone concentrations. J Clin Endocrinol Metab. 40:435–441.
5. **Paul T, Meyers B, Witorsch RJ, et al.** 1988 The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism. 37:121–124.
6. **Gardner DF, Centor RM, Utiger RD.** 1988 Effects of low dose oral iodide supplementation on thyroid function in normal men. Clin Endocrinol (Oxf). 28:283–288.
7. **Georgitis WJ, McDermott MT, Kidd GS.** 1993 An iodine load from water purification tablets alters thyroid function in man. Milit Med. 158:794–797.
8. **Namba H, Yamashita S, Kimura H, et al.** 1993 Evidence of thyroid volume increase in normal subjects receiving excess iodide. J Clin Endocrinol Metab. 76:605–608.
9. **Jubiz W, Carlile S, Lagerquist LD.** 1977 Serum thyrotropin and thyroid hormone levels in humans receiving chronic potassium iodide. J Clin Endocrinol Metab. 44:379–382.
10. **Rasmussen S.** 1974 Determination of thyroid volume by ultrasonic scanning. J Clin Ultrasound. 2:143–147.
11. **Nagataki S.** Iodine metabolism. 1990 Thyroid. 1:55–57.
12. **Nagataki S.** 1991 Autoregulation: effects of iodide. In: Braverman LE, Utiger RD, eds. The thyroid, 6th ed. Philadelphia: Lipincott; 306–312.
13. **Begg TB, Hall R.** 1963 Iodide goitre and hypothyroidism. Q J Med. 32:351–362.
14. **Paris J, McConahey WM, Owen CA, Woolner LB, Bahn RC.** 1959 Iodide goiter. J Clin Endocrinol Metab. 20:57–67.
15. **Clark OH, Lambert WR, Cavalieri RR, Rapoport B, Hammond ME, Ingbar SH.** 1976 Compensatory thyroid hypertrophy after hemithyroidectomy in rats. Endocrinology. 99:988–995.
16. **Clark OH, Cavalieri RR, Moser C, Inghbar SH.** 1990 Iodide-induced hypothyroidism in patients after thyroid resection. Eur J Clin Invest. 20:573–580.
17. **Guo Z, Narbaitz R, Fryer JN.** 1991 Effect of excess iodine in chick embryo thyroid follicles: initial inhibition and subsequent hypertrophy. J Anat. 176:157–167.
18. **Matte R, Ste-Marie LG, Comtois R, et al.** 1981 The pituitary thyroid axis after hemithyroidectomy in euthyroid man. J Clin Endocrinol Metab. 53:377–380.
19. **Stubner D, Gartner R, Greil W, et al.** 1987 Hypertrophy and hyperplasia during goitre growth and involution in rats-separate bioeffects of TSH and iodine. Acta Endocrinol (Copenh). 116:537–548.