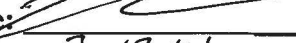
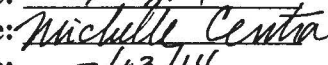


EPA Reviewer: Jonathan Leshin, Ph.D.
RASSB, Antimicrobials Division (7510P)
Secondary Review: Michelle Centra, Pharmacologist
RASSB, Antimicrobials Division (7510P)

Signature: 
Date: 3/12/14
Signature: 
Date: 3/13/14

Template version 02/06

Data Evaluation Record

PC CODE: 046905
TXR#: 1003329

DP BARCODE: 408676

STUDY TYPE: Subchronic Oral Toxicity – capsule - human; OPPTS 870.3150 [§82-1].

TEST MATERIAL (PURITY): Tetraglycine hydroperiodide (releases to iodine in water)

SYNONYMS: Iodine

CITATION: LeMar, H.J., Georgitis, W.J., McDermott, M.T. (1988) Thyroid adaptation to chronic tetraglycine hydroperiodide water purification tablet use. Madigan Army Medical Center and Fitzsimmons Army Medical Center: Journal of Clinical Endocrinology and Metabolism 80(1): 220-223. MRID 49318802

SPONSOR: US Army Medical Research and Development Command, Fort Detrick, MD

INVESTIGATORS' EXECUTIVE SUMMARY:

In a 90-day oral toxicity study (MRID 49318802), iodine in the form of tetraglycine hydroperiodide was self administered by patients as four water purification tablets dissolved in juice or water every day for ninety days. The test group was made up of eight, healthy, Caucasian volunteers; seven male and one female. Each tablet released approximately 8 mg of free iodine and thus iodine consumption was approximately 32 mg/day in addition to dietary consumption of iodine from a typical American diet.

Serum inorganic iodide increased from a level of 2.7 ± 1.0 $\mu\text{g/dL}$ to 101 ± 21 $\mu\text{g/dL}$ after ninety days of exposure. Protein bound iodide increased from 4.8 ± 0.5 $\mu\text{g/dL}$ to 27.7 ± 1.3 $\mu\text{g/dL}$ after ninety days of exposure. Urinary iodide increased from 0.276 ± 0.061 mg/day to 35 ± 4.4 mg/day after ninety days of exposure, a rise of approximately 150 fold. Radioactive iodine uptake dropped from 8-26% to below 2% after day 7 and remained below 2% through day 90. Mean serum T_3 and T_4 declined after 7 days, with T_4 remaining below baseline and T_3 recovering by the end of the treatment period. Serum TSH and TSH response to TRH rose after 7 days and remained elevated throughout the study. The average thyroid volume was increased by 37%. Neither hypo- nor hyper- thyroidism was found in any subject. For the 7 subjects available for repeat thyroid volume determinations on average 7.1 months after the study was concluded, the

thyroid volume returned to baseline. This indicates that a reversible, TSH dependent thyroid enlargement occurs in response to increased iodine load from daily use of water purification tablets.

This study is labeled **qualitative** as it is outside the parameters for a normal guideline study. It does provide useful information on the effects of excess iodine in humans, which include a form of reversible thyroid gland volume increase and decreases in T₄ levels, along with a adaptive change in T₃ levels.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:

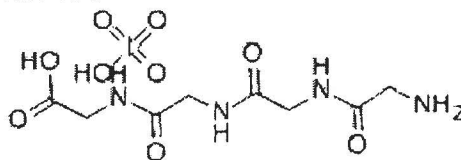
Description:

CAS # if TGAI:

Tetraglycine hydroperiodide

Tablets provided by the US Army quartermaster supply from Van Ben Industries

7097-60-1



2. Vehicle and/or positive control: Juice or water

3. Test animals:

Humans

Diet:

Typical American

Subject information:

7 male and 1 female Caucasians, age 35-47, healthy, not pregnant, euthyroid, no history of thyroid disease, chronic medical disorders, use of medications known to affect thyroid function or previous reactions to iodine.

B. STUDY DESIGN AND METHODS:

All subjects had initial evaluations for the study. Baseline levels of blood basal serum iodine, T₄, T₃, and TSH were measured. Stimulated TSH was measured twenty minutes after stimulation by TRH (TSH-20). A 24 urine sample was collected to measure baseline urinary iodine. A 24 hour radioactive iodine uptake (RAIU) was recorded after dosing with 1 μ Ci dose of ¹³¹I, with ten minute counting times. Thyroid volume was measured in the recumbent position by ultrasound.

Subjects consumed four water purification tablets dissolved in juice or water daily for 90 days in addition to their regular daily diet. Repeat serum iodine, T₃, T₄, TSH and TSH-20 and urinary iodine measurements were collected on days 7, 28 and 90. RAIU was remeasured on days 7 and 90 and thyroid volume was reassessed on days 35 and 90.

Results were expressed as mean \pm sem, with a level of p<0.05 considered statistically significant. Data was analyzed by analysis of variance (ANOVA), followed by Student-Newman-Keuls

multiple comparison tests.

II. RESULTS

A. Serum inorganic, protein-bound and urinary iodides:

Serum inorganic iodide increased from a level of 2.7 ± 1.0 $\mu\text{g/dL}$ to 101 ± 21 $\mu\text{g/dL}$ after ninety days of exposure, with saturation occurring after 28 days. Protein bound iodide increased from 4.8 ± 0.5 $\mu\text{g/dL}$ to 27.7 ± 1.3 $\mu\text{g/dL}$ after ninety days of exposure with saturation occurring after seven days. Urinary iodide increased from 0.276 ± 0.061 mg/day to 35 ± 4.4 mg/day after ninety days of exposure, a rise of approximately 150 fold. These changes are outlined in Table 1.

Table 1: Changes in serum inorganic, protein bound and urinary iodides

	Before treatment	During Treatment		
		Day 7	Day 28	Day 90
Serum				
Inorganic ($\mu\text{g/dL}$)	2.7 ± 1.0	$93 \pm 24^*$	$102 \pm 23^*$	$101 \pm 21^*$
Protein bound ($\mu\text{g/dL}$)	4.8 ± 0.5	$32.0 \pm 5.2^*$	$29.8 \pm 4.2^*$	$27.7 \pm 1.3^*$
Urine				
Iodine (mg/day)	0.276 ± 0.061	$37.2 \pm 4.4^*$	$42.5 \pm 6.5^*$	$35.0 \pm 4.4^*$

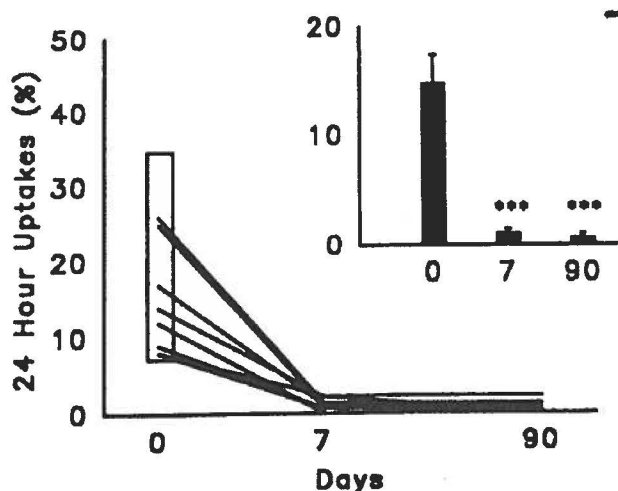
Data shown are the mean \pm sem.

* $p < 0.001$

B. Radioiodine thyroid uptake:

Three 24 hour RAIU tests were performed, before and after 7 and 90 days of treatment. Uptake dropped from 8-26% to approximately two percent after seven days and below two percent after 90 days. This data is shown in Figure 1.

Figure 1. Individual 24-hour radioactive iodine uptake before and during treatment. 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 \pm SEM are displayed in inset. ***, $P < 0.001$



C. Serum thyroid hormones:

Mean serum T₄ concentration fell slightly on day 7 and remained below pretreatment value through days 28 and 90. Mean T₃ concentration was lower than pretreatment value on day 7 but averaged above baseline on days 28 and 90. No changes were significant. Data is shown in Table 2.

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*	3.30 ± 0.33*	2.98 ± 0.50*
TSH-20	9.90 ± 0.77	14.94 ± 2.41*	18.84 ± 1.72**	16.33 ± 1.69*
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*	23.3 ± 11.3

* p<0.05

** p<0.01

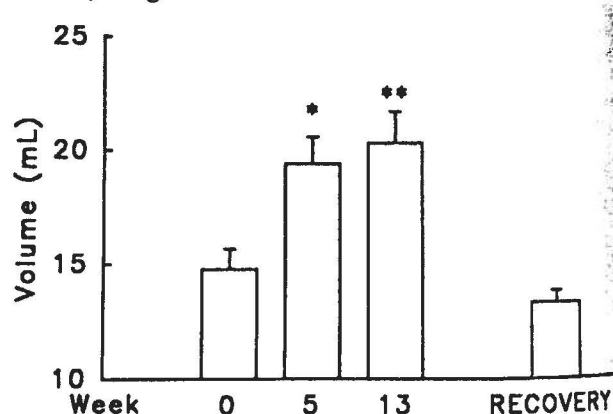
Tg = Serum thyroglobulin

D. Thyroid volume and TSH:

Serum TSH and TSH-20 values rose significantly from baseline by day 7 and remained elevated on days 28 and 90. Unstimulated TSH increased approximately doubled on average and the greatest increase in unstimulated TSH grew by three fold during the study. This subject also had the greatest change in thyroid volume of 1.8 fold. Thyroid volume increased significantly from baseline by day 35 and remained elevated through day 90. The mean increase in thyroid volume was 37%. Changes in thyroid volume and unstimulated TSH were not correlated. Those subjects available for repeat thyroid volume determinations showed a return to baseline volume during an

average of 7.1 months post treatment. TSH remained persistently above initial baseline values in all subjects, with one exception whose TSH fell below baseline but remained in the middle of the established range of treatment. Data is shown in Figure 2 and Table 2.

Figure 2: Thyroid volumes before, during and after treatment. Thyroid volume increased significantly after day 35 and enlarged slightly more after 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 \pm SEM, *, $p < 0.05$, ** $p < 0.01$



E. General observations:

No subject developed hyperthyroidism, hypothyroidism or symptomatic thyroid enlargement.

III. INVESTIGATORS' DISCUSSION AND CONCLUSIONS:

Serum inorganic iodide increased from a level of 2.7 ± 1.0 $\mu\text{g/dL}$ to 101 ± 21 $\mu\text{g/dL}$ after ninety days of exposure. Protein bound iodide increased from 4.8 ± 0.5 $\mu\text{g/dL}$ to 27.7 ± 1.3 $\mu\text{g/dL}$ after ninety days of exposure. Urinary iodide increased from 0.276 ± 0.061 mg/day to 35 ± 4.4 mg/day after ninety days of exposure, a rise of approximately 150 fold. Radioactive iodine uptake dropped from 8-26% to below 2% after day 7 and remained below 2% through day 90. Mean serum T_3 and T_4 declined after 7 days, with T_4 remaining below baseline and T_3 recovering by the end of the treatment period. Serum TSH and TSH response to TRH rose after 7 days and remained elevated throughout the study. The average thyroid volume was increased by 37%. Neither hypo- nor hyper- thyroidism was found in any subject. For the 7 subjects available for repeat thyroid volume determinations on average 7.1 months after the study was concluded, the thyroid volume returned to baseline. This indicates that a reversible, TSH dependent thyroid enlargement occurs in response to increased iodine load from daily use of water purification tablets.

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change in T₃ levels.