Thyroid Function Changes Related to Use of Iodinated Water in United States Space Program

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Abstract

Background

The National Aeronautics and Space Administration (NASA) has used iodination as a method of microbial disinfection of potable water systems in United States spacecraft and long-duration habitability modules. A review of the effects on the thyroid following consumption of iodinated water by NASA astronauts was conducted.

Methods

Thyroid function tests of all past and present Astronauts were reviewed. Medical records of astronauts with a diagnosis of thyroid disease were reviewed. Iodine consumption by space crews from water and food was determined. Serum TSH and urinary iodine excretion from space crews was measured following modification of the Space Shuttle potable water system.

Results

Mean TSH was significantly elevated in 134 astronauts who had consumed iodinated water during space flight. The serum TSH and urine iodine levels of Space Shuttle crewmembers who flew following modification of the potable water supply system did not show a statistically significant change.

There was no evidence supporting association between clinical thyroid disease and the number of space flights, amount of iodine consumed, or duration of iodine exposure.

Abstract

There was no evidence supporting association between clinical thyroid disease and the number of space flights, amount of iodine consumed, or duration of iodine exposure.

Conclusions

Pharmacological doses of iodine consumed by astronauts transiently decreased thyroid function, as reflected in serum TSH values. Although the adverse effects of excess iodine consumption in susceptible individuals are well documented, exposure to high doses of iodine during space flight did not result in a statistically significant increase in long-term thyroid disease in the astronaut population.

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Introduction

Iodine has long been recognized as an effective agent for the disinfection of drinking water (1), as it is bactericidal, virucidal, and amebicidal. It has been used for water treatment primarily in emergency situations and for disinfection of small individual water supplies. Iodine has had limited use for disinfection of domestic water supplies in the United States because of concern for long term health hazards associated with elevated iodine intake (2,3).

In persons without underlying thyroid disease, thyroid function does not appear to be adversely affected by iodine consumption of less than 500 μg daily, (4,5). The World Health Organization (WHO) has stated, however, that susceptible individuals may develop iodide goiter, hypothyroidism and hyperthyroidism after excessive iodine intake (6). The Food and Drug Administration (FDA) recommended daily iodine intake of 0.15 mg/day is similar to the recommendation of WHO, which is 0.1-0.3 mg/day. Median daily iodine intake in the USA is approximately 0.225 mg.

Few studies have been conducted on the medical effects of iodinated water. Some military personnel exposed to large iodine loads from tetraglycine hydroperiodide water purification tablets (32 mg free iodine for 3 months) developed TSH dependent thyroid enlargement. The average thyroid volumes were 37% greater at the completion of the study than at the onset (7). Two backpackers developed iodide-induced thyrotoxicosis, termed 'Travelers' Thyrotoxicosis', in association with prolonged use of iodinated preparations for water purification. One traveler used tetraglycine hydroperiodide tablets while the second used a 10% povidine-iodine

tincture. Both individuals had underlying asymptomatic autoimmune thyroid disease (8).

A recent report describes thyroid abnormalities in Peace Corps volunteers who consumed excess iodine from water purification units (9). The two-stage iodine-resin ceramic filters introduced 10 mg iodine/L into the water. With water consumption of 5-9 L per day, they consumed at least 50 mg iodine per day. The urine iodine levels averaged 11,050 μg/L. Thirty-three of 96 volunteers had thyroid dysfunction (TSH levels above and below the normal range), while 44 volunteers had enlarged thyroids.

A study of the effects of low dose oral iodide supplementation on thyroid function in normal subjects is summarized in Table 1 (4,5,10). Iodine supplementation of 0.5 mg daily above dietary intake resulted in inconsistent increases in basal and TRH stimulated serum TSH values.

Iodine has been used for microbial disinfection in the potable water systems for United States spacecraft, as well as for NASA long duration habitability studies. In 1997, a test subject in a NASA 60-day long-duration habitability study developed abnormal thyroid function tests following consumption of iodinated water.

To determine if there were adverse medical effects from the use of excess iodine in the Space Program, we reviewed thyroid function tests and iodine exposure of all astronauts at the Johnson Space Center. We also prospectively studied thyroid function tests and urine iodine levels of the crewmembers of one Shuttle flight in 1998 following removal of most of the iodine from the Shuttle potable water supply.

Methods

Spacecraft potable water disinfection

Iodine has been used in U.S. spacecraft potable water systems beginning with the Apollo lunar landing module in which tincture of iodine (12 mg/L of total iodine, iodine plus iodide) was consumed by crewmembers for an average of 2.1 days. In

the Skylab program (three manned missions 28, 59, and 84 days in length respectively, 1973-1974), iodine was added to potable water in the triiodide form (2 parts potassium iodide: 1 part iodine). As iodine was depleted, additional iodine was manually added to water storage tanks of the spacecraft, resulting in a progressive increases in iodine concentration, to levels as high as 36 mg total iodine/L in Skylab 4. In the Shuttle program (1981-present), iodine was introduced into the potable water via an iodinated anion exchange resin. This device added iodine at a ratio of ~3 parts iodine/ 1 part iodide yielding ~4 mg/L total iodine in the potable water (mg/L = ppm) (11,12).

Characteristics of Astronaut population

At the end of 1997, there were 270 Astronauts including past and present members. Medical evaluation of these astronauts included extensive evaluation prior to selection, routine annual medical examinations, and pre- and post-flight examinations (13). Thyroid function tests were included in these evaluations. However, most of these individuals were not screened for anti-thyroid antibodies.

Classification of Cases

Thyroid function test results of every member of the astronaut corps, past and present, were reviewed. The medical record of each astronaut who had been diagnosed with thyroid disease was reviewed by one of the authors (KAM). Data were available for the first space flights on 134 astronauts from the Shuttle program for whom we had thyroid function test data at five points: a routine annual examination before space flight; a preflight examination; an examination on the return day (R+0); one 3 days later (R+3); and a routine annual examination after the flight. Paired t-tests were used to determine differences in mean values of thyroid function tests at various time periods.

Iodine exposure

Exposure to iodinated water aboard spacecraft was defined as consumption of potable water that was disinfected with iodine. Astronauts had consumed approximately 2 L iodinated water/day (14). The average total iodine consumption per mission was estimated by multiplying the total iodine (mg/L) x 2 L/day x length of exposure. The length of exposure was the mission duration (Skylab and Shuttle

missions) or the number of days that the water supply contained iodine (Apollo Lunar Landing Module, Shuttle-Mir missions). The cumulative exposure for each astronaut was defined as the sum of the mission exposures. Prior exposures were not considered.

The iodine content of foods consumed on the Shuttle was measured to determine the iodine content of each food. Analysis of 467 days of Shuttle menus representing nine recent flights revealed that the mean iodine content was 0.255 +/- 0.125 mg iodine per day.

The serum TSH concentrations of a 1998 Shuttle crew were assayed from specimens obtained during flight and following landing. This flight took place after the water system had been modified to remove most of the iodine from the potable water. TSH measurements were obtained from this crew to determine whether removal of the iodine had eliminated the rise in TSH that had been previously been observed in other crews on landing day. Iodine and iodide were removed from the cold water using activated carbon and an ion exchange resin. Iodine in the hot

water was reduced to 1.5 mg/L. Consumption of hot water was limited to 0.3 L/day (0.5 mg iodine/day from water). Because urinary iodine is closely correlated with iodine intake (15,16), urine iodine levels were measured before, during, and after flight either in 24-hour pooled urine samples (μg /24 hours) or in random urine samples (μg /L).

Instrumentation and test methods

Instrumentation and test methods have varied greatly over the past 30 years. During the 1960's and early 1970's (Apollo missions), only the serum thyroxine (T4) was measured. In the mid-1970's, an in-house radioimmunoassay (RIA) for thyroid stimulating hormone (TSH) was introduced (normal<10 μU/ml). The TSH methodology changed twice in the 1980's: to a Beckman RIA method in 1980, (range 0.1-9.7 μU/ml), and to a Diagnostic Products Corporation RIA method in 1984 (upper limit of normal, 6.0 μU/ml).

In 1991, the Abbott IMx analyzer (Microparticle Enzyme Immunoassay [MEIA]) was employed with the same normal range. The current TSH is considered to be a

highly sensitive assay with a reference range of 0.47-5.01 μU/ml. We have assumed that an abnormal result in one assay (especially elevated values) would also be abnormal in another, despite individual value differences. We also recognize that in early TSH assays, hyperthyroidism could not be distinguished from euthyroidism. While all thyroid function tests were reviewed, TSH was found to represent the earliest and most sensitive marker of altered thyroid function following iodine exposure. Therefore, only TSH values were considered in this study.

Iodine levels in the Apollo lunar landing module water supplies were not measured (1969-1972, Apollo 11-17). During the Skylab missions (1973-1974), iodine levels in the water were determined by linear starch reagent optical methods. For Shuttle missions, potable water iodine levels were measured post-flight by colorimetric methods.

Urine iodine was measured by argon plasma mass spectrometer at Mayo Clinic Reference Laboratories. The normal range was 100-460 μg/24hours.

Iodine content in food was measured by a thiocyanate catalytic reduction method.

Results

Thyroid Function Tests

For the 134 Space Shuttle astronauts who had consumed iodine during space flight the mean TSH of 3.4 μU/L at R+0 was significantly higher than baseline ($p<0.001$), with return to baseline noted 3 days later, as shown in Table 2. For those individuals with TSH > 4.5 μU/ml at R+0, the increase in TSH values was more pronounced ($p<0.001$), but those values also returned to baseline at R+3.

Following the long-duration space flights of Skylab (28-84 days), astronauts' mean TSH values were significantly elevated at R+3 ($p<0.05$) as well as R+0. Six astronauts serving on the Russian Space Station Mir (as of 12/31/97) consumed water disinfected with silver followed by pasteurization. Consumption was split into two periods, the Shuttle flight to Mir Space Station, and the Shuttle flight returning from Mir. Their serum TSH values did not exhibit the statistically significant

elevation in TSH at R+0 seen in astronauts who have spent a longer uninterrupted period consuming iodinated water.

The crewmembers of the 1998 space flight who consumed markedly reduced iodine in their drinking water had no significant differences in serum TSH values compared to the preflight and postflight annual medical exams. The data are shown in Table 2.

Urine Iodine Levels

During the 1998 space flight, astronauts collected either random urine samples or 24-hour pooled urine specimens for urine iodine assay. Baseline pre-flight urine iodine levels averaged 369 μg /24 hours. Spot urine iodine values ranged from 292-1124 μg /L, averaging 701 μg /24 hours. On R+0, the urine iodine levels rose sharply, averaging 3835 μg /24 hours. The deiodinator had been dismantled and stowed for deorbit prior to filling the drink bags. Thus, during oral fluid loading for re-entry, the crew consumed approximately 2 liters of fully iodinated water (3.6 mg total iodine/L), for an iodine consumption of ~7.2mg. This is shown in Table 3.

Clinical thyroid disease (Table 4)

15 cases of thyroid disease were diagnosed in 270 astronauts (11/234 males and 4/36 females). Eight individuals (6 males, 2 females) were diagnosed with thyroid disease prior to space flight. Diagnoses included Hashimoto's thyroiditis (5), subclinical hypothyroidism (4), hypothyroidism (1), goiter (1), non-toxic nodular goiter (1), and papillary carcinoma (1). Seven cases occurred in crewmembers after iodine exposure during space flight and included Hashimoto's thyroiditis (2), subclinical hypothyroidism (2), hypothyroidism (2), nontoxic nodular goiter (2), and adenoma (1). Some individuals had more than one diagnosis. Because of the extreme variation in iodine exposure during space flight, the data were divided into missions, exposure days, iodine levels, and total mission intake. There was no association between the incidence of thyroid disease and the number of space flights (0-6), the amount of iodine consumed or the duration of iodine exposure. There was no evidence of an association between iodine exposure and subsequent thyroid disease in any subgroup defined by position (pilot vs. mission specialist) or gender. Six crewmembers were exposed to iodine for more than 30 days

continuously (Skylab 3 and 4). These crewmembers showed no association between iodine exposure and subsequent thyroid disease.

Discussion

The thyroid responds to ingestion of large quantities of iodine by a transient decrease in thyroid hormone synthesis, the acute Wolff-Chaikoff effect, ascribed to an increase in intrathyroidal iodide (3,17). The escape from or adaptation to excess iodine occurs in approximately 48 hours and normal hormone synthesis resumes, as a result of a decrease in the active transport of iodide from the plasma into the thyroid, thereby reducing the intrathyroidal iodide concentration to levels compatible with normal thyroid hormone synthesis. The escape from the acute Wolff-Chaikoff effect has recently been reported to be due, at least in part, to a decrease in the sodium/iodide symporter mRNA and protein (18). Excess iodine also decreases release of thyroid hormones from the gland, contributing to the temporary slight decrease from baseline values of the serum T4 and T3 concentrations (19). A compensatory small rise in serum TSH above baseline maintains normal thyroid

function. Thus, in normal individuals, thyroid function tests are preserved within the normal range even during long term exposure to excess iodine (20,21).

The potable water aboard the Space Shuttle contained a mean concentration of 3.6 mg iodine/L. With an average daily consumption of 2 L water, astronauts ingested approximately 7.2 mg total iodine/day for the duration of the mission. These pharmacological doses of iodine were sufficient to transiently decrease thyroid function, as reflected in the elevated serum TSH concentrations upon return to earth. The exposure to high doses of iodine during space flight was not associated with long-term thyroid disease in this population.

The early increase in TSH secretion, seen in the crewmembers returning from space flight, was probably due to iodine-induced small decreases in serum T4 and a compensatory rise in serum TSH as an adaptive response to the large doses of circulating iodine. Unfortunately, serum T4 and free T4 measurements were not consistently available to determine whether small decreases within the normal range occurred during iodine exposure. That the increase in serum TSH was due to

iodinated water consumed during space flight is supported by the absence of a TSH increase upon return to earth (R+0) in the 1998 space flight where interim measures had significantly reduced the iodine levels in the drinking water. It is also supported by an absence of TSH changes at R+0 in the MIR astronauts who consumed iodine only briefly during the Shuttle flights to and from the MIR Space Station.

Although subjects with normal underlying thyroid function remain euthyroid during chronic iodine exposure, there exist susceptible individuals in whom excess iodine will induce clearly adverse effects. Those individuals with underlying thyroid disease are very sensitive to large doses of iodine and may not maintain normal thyroid function, manifested most commonly as iodine-induced hypothyroidism (22,23). It is possible that all individuals who develop thyroid dysfunction when exposed to large quantities of iodide have an underlying defect in thyroid function, which prevents the normal adaptation to excess iodide (24,25). A summary of iodine induced thyroid disorders is presented in Table 5 (26,27). Hashimoto's thyroiditis is the most common iodine-induced thyroid disorder in previously euthyroid individuals and is more common in areas of iodine sufficiency than in areas of inadequate iodine

intake (28). The presence of anti-thyroid antibodies (thyroid peroxidase and thyroglobulin antibodies) is commonly used to detect patients with this disorder (29,30). Most members of the astronaut corps have not been screened for anti-thyroid antibodies.

Iodide-induced hyperthyroidism has occasionally followed the use of iodides to treat endemic iodine-deficiency goiter and it can occur in older patients with nodular thyroid disease in iodine sufficient areas (31,32,33). International astronauts will fly aboard the International Space Station. While a number of these astronauts come from iodine-deficient regions in Western and Eastern Europe and Russia, most individuals spend one or more years training in the U.S. prior to their spaceflight, where they consume an iodine-sufficient American diet. There is no evidence that iodine-induced hyperthyroidism has occurred in any of the international astronauts.

It is difficult to define an upper limit of normal for daily iodine intake. The issue is what is normal, what is acceptable, and what is clearly excessive. An acceptable level of iodine intake would be one that is unusually high, but is also an uncommon

cause of thyroid disease, whereas an excessive iodine intake would be one that leads to definite thyroid disease in a significant proportion of the population. It must be recognized that what is acceptable for some individuals is excessive for others.

It appears that an iodine intake less than or equal to 1.0 mg/day is probably safe for the majority of a population, but may cause adverse effects in occasional individuals. Those most likely to respond adversely are those who have lived in endemic goiter areas or who for other reasons have a habitually low intake of iodine and those with other thyroid disorders (such as Hashimoto's thyroiditis, Graves' disease, or non-toxic nodular goiter). The maximum tolerable level of iodine for most people appears to range from somewhat above the RDA (i.e. about 0.2 mg/day) to 1.0 mg/day (34). A chronic daily intake of 2 mg of iodine should be regarded as excessive and potentially harmful (3,17,35).

A consulting panel of three of the authors (JTD, LEB, JBS) recommended that the total amount of iodine ingested by crewmembers be limited to a maximum of 1.0 mg/day for Space Shuttle operations. This limit includes iodine from all sources

including dietary intake and potable water consumption. In order to limit the potable water consumption of iodine, an interim iodine removal cartridge (an anion exchange resin) was installed to remove most of the iodine from the drinking water. A resin device is currently being developed that efficiently reduces iodine from the ~4 mg/L. The target value is 0.25 mg/L for both the chilled and hot water.

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Table 1: Effects of Low Dose Oral Iodide Supplementation on Thyroid Function in Normal Subjects

Investigator (ref #)	Iodide, mg/day	TSH	TSH Response to TRH	T4/Free T4	T3
Paul (5)	0.25	No effect	No effect	No effect	No effect
Paul (5)	0.5	No effect	No effect	No effect	No effect
Gardner (4)	0.5	No effect	↑	↓ /	Not done
Chow (10)	0.5	↑	Not done	/ ↓	Not done
Paul (5)	1.5	↑	↑	↓ /	↓
Gardner (4)	1.5	↑	↑	↓ / ↓	No effect
Gardner (4)	4.5	↑	↑	↓ / ↓	No effect

Table 2: Serum TSH Values in Astronauts with Iodine Exposure

Mission	Number of Subjects	Mean Days in Space exposed to Iodine (Range)	Total Iodine exposure (mg)	TSH Ref. Range (μU/L)	TSH Pre-flight Annual	TSH L-10	TSH R+0	TSH R+3	TSH Post-flight Annual	Incidence of thyroid disease	Comments
Skylab	9	57 (28-84)	3061	0-10	4.2	4.9	8.4*	8.6	4.2	none	Annual exam 3 years later
Shuttle^ STS-1-STS-51L	134	6 (2-10)	72.1	Varied 0.1-9.7 0-6.0	2.6	2.8	3.4*	2.5	2.4	7/134	
Shuttle^ STS-26-STS-87		9 (4-17)	67.2	Varied 0-6.0 0.4-5.1							
Shuttle-Mir	6	9 (8-10)	60.8	0.4-5.1	2.0	2.2	2.7	1.8	1.5	0/6	Iodine consumption split by stay on Mir
1998 Shuttle Mission#	7	17	8	0.4-5.1	2.1	2.2	2.2	1.7	1.4	0/7	No iodine in chilled water, 1.5 mg/L iodine in hot water, consumption limit 0.3 L/day

^: If baseline TSH >4, response at R+0 is exaggerated.
*: Mean TSH at R+0 significantly different from all other examinations (paired t-test, $p<0.001$)
#: ~2L of iodinated water (3.6 mg iodine/L) consumed in drink bags during deorbit

Table 3: Mean Urine Iodine Values Prior to During, and After 1998 Spaceflight

	μg/24 hr*	μg/L*
Preflight	361 (n=7)	276 (n=7)
During Flight	701 (n=3)	648 (n=5)
Return Day (R+0)	3835 (n=5)	4452 (n=7)
Postflight (R+3)	782 (n=2)	409 (n=7)

*Some crewmembers provided both spot and 24-hour specimens in-flight.

Iodine Concentration in galley water: chilled water: <0.05 mg/L, hot water: 1.5 mg/L (consumption limit 0.3 L/day)

Normal range: 100-460 μg/24 hours

Table 4: Thyroid Disorders as a Function of Iodine Exposure in Astronauts

Iodine exposure	None^	One or more spaceflights
# cases thyroid disease	8	7
Types of thyroid disease*	Hashimoto's thyroiditis ----------5 Subclinical hypothyroidism------4 Hypothyroidism------------------1 Non-toxic nodular goiter---------1 Goiter----------------------------1 Papillary carcinoma--------------1	Hashimoto's thyroiditis--------2 Subclinical hypothyroidism----4 Hypothyroidism--------------2 Non-toxic nodular goiter------ 2 Adenoma---------------------1

^: Onset of thyroid disease prior to initial spaceflight iodine exposure

*: Some individuals had more than one diagnosis

Table 5: Iodine-Induced Thyroid Disorders

Iodine-induced hypothyroidism or goiter

No underlying thyroid disease

Fetus and neonate, mostly preterm

Secondary to transplacental passage of iodine and exposure of newborn infants to topical or parenteral iodine-rich substances.

Infant

Occasionally reported in infants drinking iodine-rich water (China).

Adult

Frequently reported in Japanese subjects with high iodine intake (Hashimoto's thyroiditis has been excluded).

Elderly

Reported in elderly subjects with possible defective organification and autoimmune thyroiditis.

Chronic nonthyroidal illness

Cystic fibrosis

Chronic lung disease (Hashimoto's thyroiditis was not excluded).

Chronic dialysis treatment

Thalessemia major

Underlying Thyroid Disease

Hashimoto's thyroiditis

Table 5: Iodine-Induced Thyroid Disorders

Euthyroid patients previously treated for Graves' disease by ^{131}I, thyroidectomy, or antithyroid drugs

Subclinical hypothyroidism, especially in the elderly

After subacute, painful thyroiditis

After postpartum lymphocytic thyroiditis

After hemithyroidectomy for benign nodules

Euthyroid patients with a previous episode of amiodarone-induced destructive thyrotoxicosis

Euthyroid patients with a previous episode of interferon-alpha induced thyroiditis

Iodine Plus Other Potential Goitrogens

Sulfisoxazole: cystic fibrosis

Lithium

Sulfadiazine (?)

Iodine-induced hyperthyroidism

Iodine supplementation for endemic iodine deficiency goiter

Iodine administration to patients with euthyroid Graves' disease, especially those in remission after antithyroid drug therapy

Table 5: Iodine-Induced Thyroid Disorders

Iodine administration to patients with underlying thyroid disease (more common in areas in marginal iodine sufficiency)

Nontoxic nodular goiter

Autonomous nodule

Nontoxic diffuse goiter

Iodine administration to patients with no recognized underlying thyroid disease

Adapted from Roti E, Vagenakis AG: Effect of excess iodine: clinical aspects. In Braverman LE, Utiger RD (eds). Werner and Ingbar's The Thyroid, 7th edition. Philadelphia: JB Lippincott, pp. 316-327, 1996.