

COMPARISON OF THE EFFECTS OF IODINE AND IODIDE ON THYROID FUNCTION IN HUMANS

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Concerns have been raised over the use of iodine for disinfecting drinking water on extended space flights. Most fears revolve around effects of iodide on thyroid function. Iodine (I_2) is the form used in drinking-water disinfection. Risk assessments have treated the various forms of iodine as if they were toxicologically equivalent. Recent experiments conducted in rats found that administration of iodine as Γ (iodide) versus I_2 had opposite effects on plasma thyroid hormone levels. I_2 -treated animals displayed elevated thyroxine (T_4) and thyroxine/triiodothyronine (T_4/T_3) ratios, whereas those treated with Γ displayed no change or reduced plasma concentrations of T_4 at concentrations in drinking water of 30 or 100 mg/L. The study herein was designed to assess whether similar effects would be seen in humans as were observed in rats. A 14-d repeated-dose study utilizing total doses of iodine in the two forms at either 0.3 or 1 mg/kg body weight was conducted with 33 male volunteers. Thyroid hormones evaluated included T_4 , T_3 , and thyroid-stimulating hormone (TSH). TSH was significantly increased by the high dose of both I_2 and Γ , as compared to the control. Decreases in T_4 were observed with dose schedules with Γ and I_2 , but none were statistically significant compared to each other, or compared to the control. This human experiment failed to confirm the differential effect of I_2 on maintenance of serum T_4 concentrations relative to the effect of Γ that was observed in prior experiments in rats. However, based on the elevations in TSH, there should be some concern over the potential impacts of chronic consumption of iodine in drinking water.

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Iodine (I_2) has been used successfully in the final disinfection of drinking water in the space shuttle program. As space station missions are extended in time and the manned space program begins to focus on the moon or Mars, very long exposures to iodine can be anticipated. In practice, a small residual of iodine (0.5 to 2 mg/L) is added to prevent outgrowth of organisms in the storage and dispensing units on the space station. Other means of disinfecting present other hazards (chlorine gas, ozone) that are unacceptable in a confined space.

Iodine has not been frequently employed in domestic water supplies because of fears of inducing some longer term health hazards that are associated with elevated intakes of iodine, most specifically congenital goiter (Wolff, 1969; Carswell et al., 1970). The question remains as to how much iodine can remain in the water that is consumed without resulting in a health hazard to the humans consuming the water.

Experiments conducted in rats found that administration of iodine as I^- (iodide) versus I_2 had opposite effects on plasma thyroid hormone levels (Sherer et al., 1991). I_2 -treated animals displayed elevated thyroxine (T_4) and thyroxine/triiodothyronine (T_4/T_3) ratios, whereas those treated with I^- displayed no change or reduced plasma concentrations of T_4 at concentrations in drinking water of 30 or 100 mg/L. Substantial differences were also observed in the uptake and distribution of radioiodine in the body depending upon whether it was administered as I^- or I_2 (Thrall & Bull, 1990; Thrall et al., 1992a). Further study revealed that this effect was attributable in large part to the reaction of I_2 with metabolites of T_4 in the gut of the rat to resynthesize T_4 (Thrall et al., 1992b). These data were in sharp contrast to the view that I_2 and I^- are essentially equivalent in their effects on thyroid function (Gilman et al., 1990).

The relative rate of thyroid hormone metabolism in humans and rats is known to be significantly different, primarily because of a greater degree of binding of the hormone to plasma proteins in humans. The turnover time of T_4 in humans varies between 5 and 9 d, whereas it is 12–24 h in rats (Hayes, 1989). This would mean that the concentrations of metabolites of thyroid hormones in the gut and available for reaction with I_2 should be significantly lower in humans than in rats.

Two experiments were designed to assess whether similar effects would be seen in humans as were observed in rats. The first of these was a rising dose tolerance study, which examined the thyroid status of three groups of male volunteers ($n = 31$). These individuals were randomly assigned to receive 5 single doses of water containing either I^- or I_2 at increasing levels of 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, and finally 1 mg/kg body weight. A control group was provided distilled water with concentrations of NaCl matched to NaI and phosphate buffer as in the treatment groups. No substantive or statistically significant differences were detected for serum triiodothyronine (T_3), T_4 , thyroid-stimulating hormone (TSH), or T_4/T_3 among the treatment groups. Thus, it was concluded that single acute doses of I_2 or I^- up to 1 mg/kg of body weight have no apparent effects on thyroid func-

tion in normal male humans (data not shown). The second experiment was a 14-d repeated-dose study utilizing total doses of iodine in the 2 forms at either 0.3 or 1.0 mg/kg body weight. The methodology and results of this experiment are presented herein.

METHODS AND MATERIALS

Study Population

Male students attending Washington State University (WSU), and qualifying for health care services at the WSU Student Health Center, were eligible for inclusion in the experiment. Volunteers were required to complete a brief medical history using a standardized checklist. Individuals reporting a history of any of the following conditions were excluded from further consideration as study subjects: thyroid, liver, kidney, or heart disease/dysfunction; malabsorption problems; porphyria; anorexia; gallbladder tests or corticosteroid use within the prior 2 mo; surgery within the prior 6 mo; allergic reaction to iodine or shell fish.

Physical examinations were completed on the remaining volunteers. The study physician carefully screened for any indication of thyroid dysfunction (i.e., nodules, goiters). Standard chemistry panels for blood [glucose, blood urea nitrogen (BUN), creatinine, uric acids, calcium, phosphorus, cholesterol, triglycerides, total protein, albumin, globulin, albumin to globulin ratio (AGR), total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactic dehydrogenase (LDH), sodium, potassium, and chloride] and urine were completed, as well as T₄, T₃, and TSH levels to verify normal thyroid function. As an additional precaution, potential subjects were given a thyroid autoantibody titer test as a screening check for asymptomatic thyroid conditions. If the study physician found no reason to suspect an individual would respond adversely to the proposed I₂ or I⁻ treatments, study enrollment was initiated.

Subject Requirements

Subjects were required to sign an informed consent form, which detailed the study procedures and restrictions. To minimize potential confounding, all subjects were non-tobacco users, and were required to eliminate alcohol, medications (prescription and over the counter), and goitrogen vegetables (turnips, rutabagas, cabbage, cauliflower, brussels sprouts, and broccoli) from their diet for at least 2 d prior to dosing, and throughout the experiment.

Treatment Groups, Dosing Amounts, and Procedures

Thirty-five subjects were randomly assigned to one of five treatment groups: either a low- or high-dose I₂ treatment, a low- or high-dose I⁻ treatment, or a control group. Dose types and amounts are presented in

Table 1. Thirty-three subjects completed all phases of the study, yielding a 94.3% (33/35) completion rate.

All procedures were performed at WSU Student Health Center. Subjects, the study physician, and laboratory staff were blinded as to the treatment group status of each individual. Subjects assigned to the I_2 treatment groups received 14 consecutive doses of I_2 in phosphate buffer over a 14-d period. Matched doses of I^- in phosphate buffer were administered to the I^- treatment groups. All subjects were dosed at exactly the same time each day over the 14-d period. To help ensure that subjects were blinded as to their treatment group status, controls received distilled water with concentrations of NaCl matched to the osmolar concentrations of NaI in the high-dose group. Control and NaI solutions were tinted with yellow food coloring and put in brown pharmacy bottles so that all treatment group doses were approximately the same color.

A significant but consistent amount (25%) of I_2 was converted to I^- in the preparation of the stock solutions. On each of the first 2 d of the study, subjects in the high-dose I_2 group received I_2 doses equal to 1 mg/kg body weight (i.e., 1.3 mg total iodine/kg). Subsequently, the dose of I_2 administered on d 3 through 14 was adjusted to 0.75 mg/kg/d (dose of 1 mg total iodine/kg/d). The elevated dose in the first 2 d led to a slightly larger time-weighted average dose in the high-dose I_2 group (1.05 mg/kg/d) than in the high-dose I^- group. The time-weighted average for total iodine for the low-dose I_2 group, however, was consistently greater (0.375 mg/kg/d) than in the I^- group (0.3 mg/kg/d). The data are provided as total iodine doses in tables and graphs. Iodine concentrations were determined using the leuco crystal violet method (Kinman, 1985), and iodide was measured utilizing an iodide specific electrode. The dose was adjusted to the body weight of each individual by appropriate changes in the volume of the stock solutions (approximately 200 mg I_2 /L for the high-dose group, and 70 mg I_2 /L for the low-dose group).

Blood Collection Ten milliliters of blood was drawn from each subject four times. Blood drawn immediately prior to dose 1 served as the baseline measure. The remaining draws were taken 2 h postdose on d 7, 2 h postdose on d 14, and 24 h following the final (14th) dose: d 0, d 7.083, d 14.083, d 15.

TABLE 1. Treatment Groups and Dose Amounts

| Treatment groups | <i>n</i> | Total iodine dose | Phosphate buffer (pH = 6.95) |
|----------------------------|----------|------------------------------|------------------------------|
| Iodine (I_2) low dose | 6 | 0.3 mg I_2 /kg body weight | 1.00 mM |
| Iodine (I_2) high dose | 7 | 1.0 mg I_2 /kg body weight | 3.33 mM |
| Iodide (I^-) low dose | 6 | 0.3 mg I^- /kg body weight | 1.00 mM |
| Iodide (I^-) high dose | 7 | 1.0 mg I^- /kg body weight | 3.33 mM |
| Control | 7 | 1.0 mg NaCl/kg body weight | 3.33 mM |

Urine Collection Urine samples were collected at baseline, and at 2, 24, 48, 72, and 240 h following the final dose to assess the excretion rate of Γ^- in the urine. Dietary salt intake was not restricted because the doses of iodine administered during this study rendered the amount derived from consuming iodized salt to insignificant amounts.

Subject Evaluation and Follow-Up Subjects were monitored for adverse reactions and evidence of toxicity each day. An exit physical examination was required of all subjects 11 d following the final dose (d 25). This included a thyroid examination, vital signs, and standard chemistry panels for blood (as previously described) and urine, to verify that all values including T_4 , T_3 , and TSH approximated the values obtained during each subject's entrance physical examination.

Analyses

Blood Analysis Total plasma T_4 , T_3 , and TSH levels were measured with chemiluminescence immunometric assay methods using the materials and methods provided in Nichols Institute Diagnostics kits (Nichols Institute Diagnostics, San Juan Capistrano, CA). These values were compared with a standard curve prepared with specific validated hormone standards. Patient hormone levels were determined directly from each standard curve (logit-log data calculations). Quality control procedures were performed during every assay, and included validated controls (Lyphochek obtained from BioRad ECS, Anaheim, CA) with high, normal, and low hormone levels. Intra-assay and interassay variability was calculated for the quality control samples with every assay. Interassay standard deviation was calculated by analysis of variance and was compared with the average result obtained on all previous assays. All samples were run in duplicate.

Urinalysis Excretion of Γ^- in the urine was determined indirectly by normalizing results with creatinine concentration of each subject's urine sample. Creatinine was measured using a diagnostic kit purchased from Sigma Chemical Co. (St. Louis, MO). Γ^- concentration of the subject's urine sample was then determined using an Γ^- selective electrode in combination with a double junction reference electrode (Orion Research Co., Boston, MA). Standard curves were prepared from samples containing 0.1 to 10 μM Γ^- . Urine samples were diluted (1:10) with double-distilled, deionized water, and electrode measurements were then compared to the standard curve. Combining the results of the creatinine study and Γ^- probe, a daily rate of Γ^- excretion was calculated.

Statistical Analysis Statistical analyses were conducted using SAS software (SAS Institute, Inc., Cary, NC). Data were analyzed as a completely randomized design with a one-way treatment structure (treatment group) with repeated measures. If a time by group interaction was detected, group effects were analyzed at each time period. Tests of least signifi-

cance difference were used to test for differences among treatment group means if analysis of variance (ANOVA) p values were $\leq .05$.

RESULTS

All subjects were male Caucasians, and ranged in age from 20 to 31 yr, with a mean age of 23.4 yr. There was no significant difference in age or body mass index between the five treatment groups.

Significant effects became apparent with repeated administration of doses of 0.3 or 1 mg/kg body weight for a 14-d period. Most of the effects relate to thyroid hormone status of the individuals, but there were also more nonspecific effects of I_2 that became apparent in this experiment. A standardized questionnaire self-administered following the final dose on d 14 discerned reports of "burned throat" unique to the I_2 treatment groups. Four of the six (66.7%) individuals in the low-dose I_2 treatment group reported a burning sensation in the throat, while five out of seven (71.4%) in the high-dose I_2 group reported a similar phenomenon. This irritation was not evident on physical examination and therefore cannot technically be termed a chemical burn. Clinical chemistries and physical examinations failed to identify any effects of either I_2 or Γ that were unrelated to thyroid function.

Figures 1 through 4 graphically depict the mean and standard error of the mean (SEM) for T_4 , T_3 , TSH, and the T_4/T_3 ratio, respectively, as measured at baseline, d 7, d 14, and d 15. The mean from the exit physical examination conducted on d 25 is also presented for each thyroid hormone measured. The top panel of each figure compares the low- and high-dose Γ groups with the control; likewise, the bottom panel compares the low- and high-dose I_2 groups with the control.

Table 2 presents the ANOVA for repeated measures outcomes for each thyroid hormone. Although none of the overall group effects were statistically significant, interaction due to variation of treatment groups over time was detected within the T_3 and TSH measures, therefore requiring univariate analysis of these two measures at each time point. The univariate analysis of T_3 detected no significant differences among group means at any of the individual time points (Figure 2).

Table 3 presents the univariate ANOVA of TSH at each time point. Statistically significant increases were observed in both the high-dose I_2 group and the high-dose Γ group, as compared to the control on d 15. At the lower doses, neither form of iodine produced increases that were statistically significant. However, there was a consistent trend toward an increase with all doses, which is difficult to ignore. TSH levels in each treatment group did largely return to control levels 11 d after treatment was suspended (Figure 3).

Urinary excretion of Γ was utilized primarily to be certain that I_2 was cleared from the system promptly after suspension of treatments. In Figure

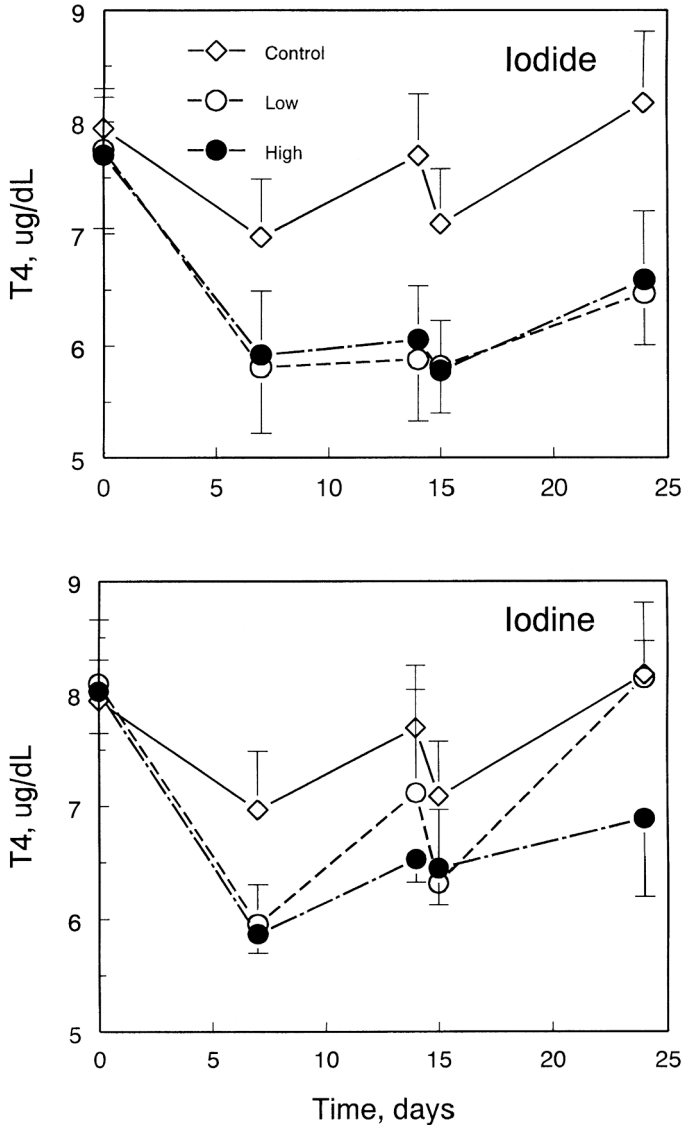


FIGURE 1. Effects of 14 daily low doses (0.3 mg/kg body weight) or high doses (1.0 mg/kg body weight) of iodide (top panel) or iodine (bottom panel) on serum thyroxine (T₄) (\pm SEM), as measured at baseline, d 7, d 14, d 15, and d 25, compared with control group.

5 it can be seen that the excretion of iodine in steady state had neared the theoretical maximum of the administered dose with all doses of I₂ when examined 24 h following the last dose of I₂. Within 72 h, the urinary excretion of I⁻ had essentially converged with the levels seen in control subjects. These data confirm the accuracy of the dosing schedule and demonstrate that the subjects complied with the dosing schedule.

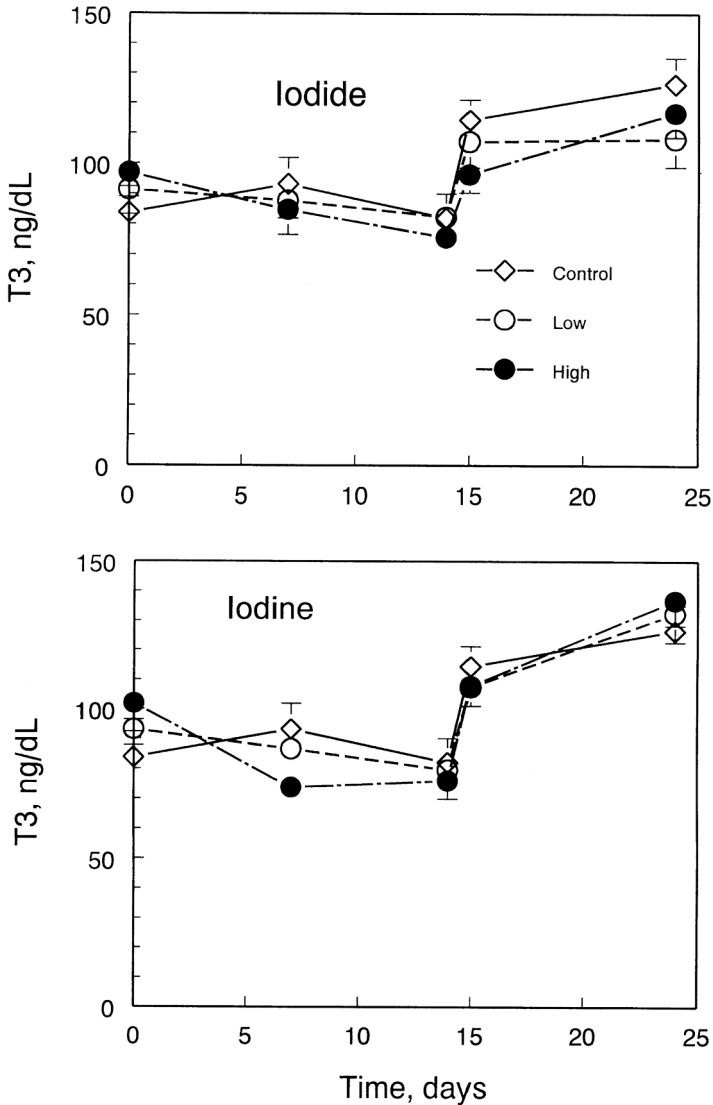


FIGURE 2. Effects of 14 daily low doses (0.3 mg/kg body weight) or high doses (1.0 mg/kg body weight) of iodide (top panel) or iodine (bottom panel) on serum triiodothyronine (T₃) (±SEM), as measured at baseline, d 7, d 14, d 15, and d 25, compared with control group.

DISCUSSION

Both specific and nonspecific effects of iodine were noted in this experiment. I₂ produced the only nonspecific effect of importance, the sensation of a “burned throat.” This effect might be expected from consumption of I₂, since high concentrations are known to damage mucous membranes (Gosselin et al., 1976). However, this effect was not reflected

in clinical observations, so it should not be considered a chemical burn as such. More than likely it reflects a significant degree of irritation to the mucous membranes that is more closely related to the concentrations of the solutions of I₂ that were administered rather than the actual dose of I₂. High concentrations were used in this study primarily for the purpose of

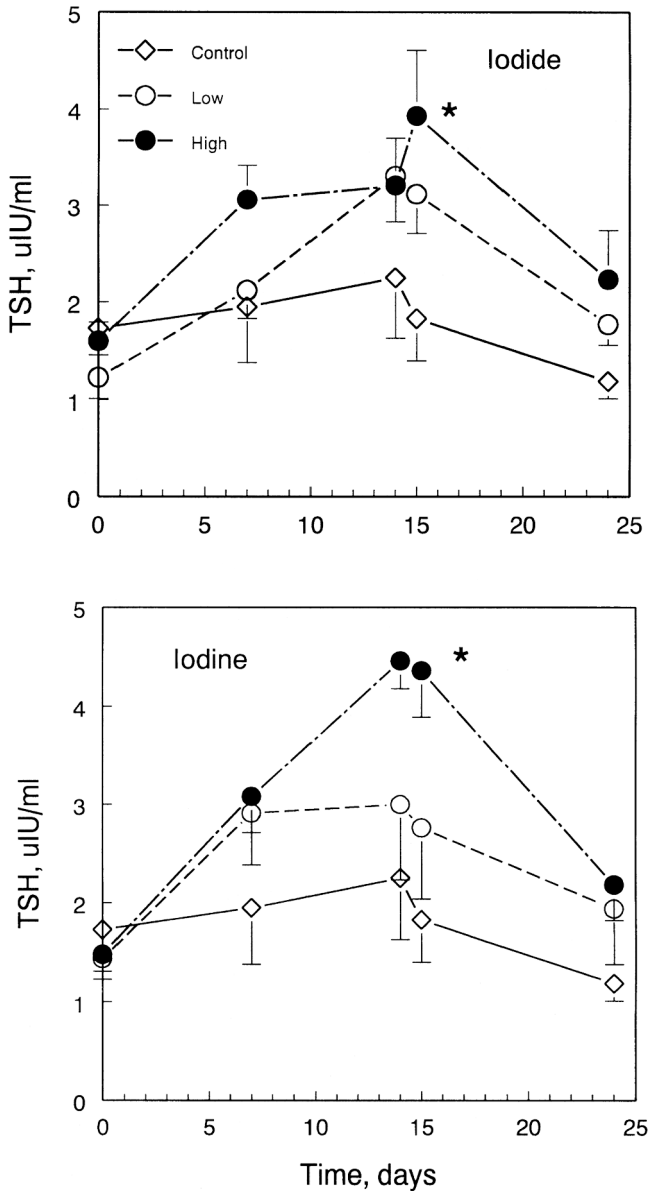


FIGURE 3. Effects of 14 daily low doses (0.3 mg/kg body weight) or high doses (1.0 mg/kg body weight) of iodide (top panel) or iodine (bottom panel) on thyroid-stimulating hormone (TSH) (\pm SEM) as measured at baseline, d 7, d 14, d 15, and d 25, compared with control group.

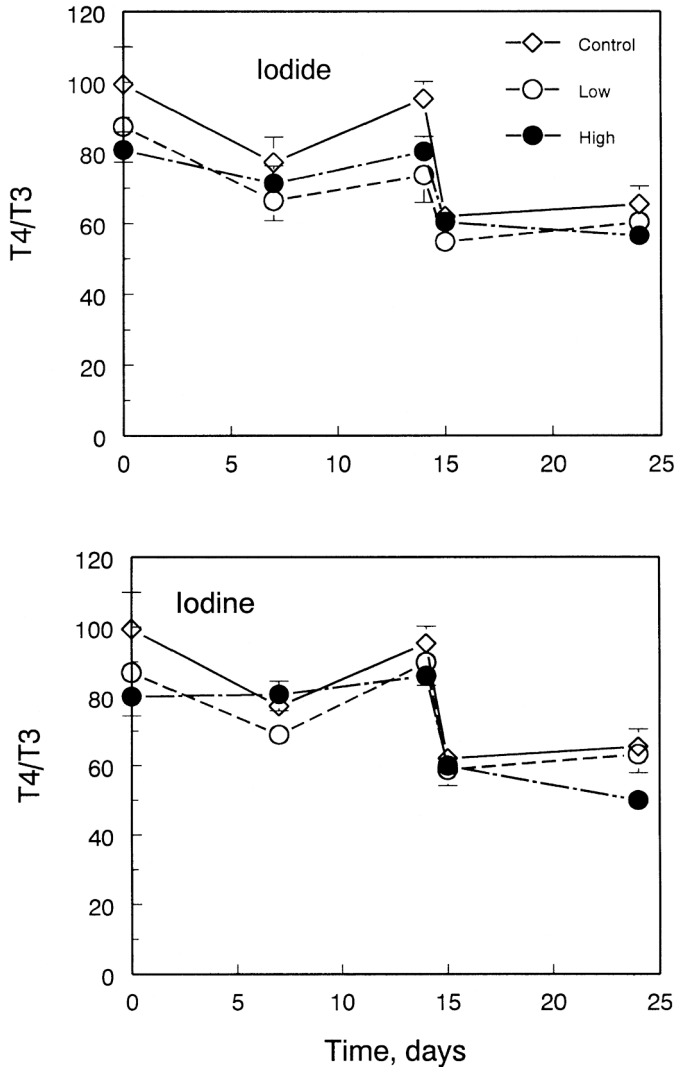


FIGURE 4. Effects of 14 daily low doses (0.3 mg/kg body weight) or high doses (1.0 mg/kg body weight) of iodide (top panel) or iodine (bottom panel) on serum triiodothyronine/thyroxine (T_4/T_3) ratio (\pm SEM), as measured at baseline, d 7, d 14, d 15, and d 25, compared with control group.

ensuring compliance by observing the actual consumption of the water. It should be noted that 70 and 200 mg/L concentrations of I_2 would never be achieved in space station water.

The daily administration of repeated doses of I_2 and I^- in the range of 0.3 to 1 mg total iodine per kilogram of body weight for a period of 14 d does induce changes in thyroid hormone status. Decreases in T_4 were observed with dose schedules with I^- and I_2 , but none were statistically

TABLE 2. Analysis of Variance for Repeated Measures: *p* Values

| Thyroid hormone | Time effect | Time by group effect | Group effect |
|--------------------------------|-------------|----------------------|--------------|
| T ₄ | .0001 | .1622 | .4332 |
| T ₃ | .0001 | .0031 | .9742 |
| TSH | .0001 | .0008 | .1255 |
| T ₄ /T ₃ | .0001 | .1133 | .3040 |

significant compared to each other, or compared to the control. TSH was significantly increased by the high dose of both I₂ and I⁻, but in this case the effects of the high-dose schedule of I₂ were substantively greater than that seen with I⁻. It may well be that these differences do reflect some underlying differences between I₂ and I⁻, but the statistical power of this experiment does not allow a clear conclusion in this area.

It was anticipated from prior studies in rats (Sherer et al., 1991; Thrall & Bull, 1990; Thrall et al., 1992a, 1992b) that there would be some divergence between the effects of iodine administered as I₂ versus I⁻. It was predicted that at some low dose of iodine, administration of I₂ would preserve or even increase the levels of circulating T₄, and would increase the T₄ to T₃ ratio. There is no clear indication of such a differential effect in the present study. There may be several reasons for this divergence. First, it is quite clear that the rate of thyroid hormone turnover in humans is much less than that observed in rodents (Gilman et al., 1990). This would result in lower concentrations of thyroid hormone metabolites that would be available in the gastrointestinal tract for reaction with administered I₂. Thus, the doses of iodine chosen may have been too high relative to the levels of available substrate. In this case, any effect due to resynthesis of T₄ may simply have been too small to detect when embedded in the well-established effect of decreased T₄ as a result of the increased consumption of total iodine. A second possibility could be inadequate amount of substrate available in the

TABLE 3. TSH (μIU/ml) Univariate Analysis of Variance

| Treatment group | Baseline, <i>p</i> = .5858, mean ± SEM | Day 7, <i>p</i> = .2034, mean ± SEM | Day 14, <i>p</i> = .0880, mean ± SEM | Day 15, <i>p</i> = .0309, mean ± SEM |
|------------------------------------|--|---|--|--|
| Iodine (I ₂) low dose | 1.44 ± 0.21 | 2.91 ± 0.53 | 2.99 ± 0.77 | 2.76 ± 0.72 |
| Iodine (I ₂) high dose | 1.48 ± 0.17 | 3.07 ± 0.37 | 4.46 ± 0.28 | 4.36 ± 0.47 ^a |
| Iodide (I ⁻) low dose | 1.23 ± 0.22 | 2.11 ± 0.29 | 3.32 ± 0.48 | 3.12 ± 0.41 |
| Iodide (I ⁻) high dose | 1.60 ± 0.19 | 3.06 ± 0.36 | 3.21 ± 0.49 | 3.93 ± 0.68 ^a |
| Control | 1.73 ± 0.27 | 1.94 ± 0.57 | 2.24 ± 0.62 | 1.83 ± 0.43 |

Note. SEM, standard error of the mean.

^aSignificantly different from control group via least significant difference test, *p* < .02.

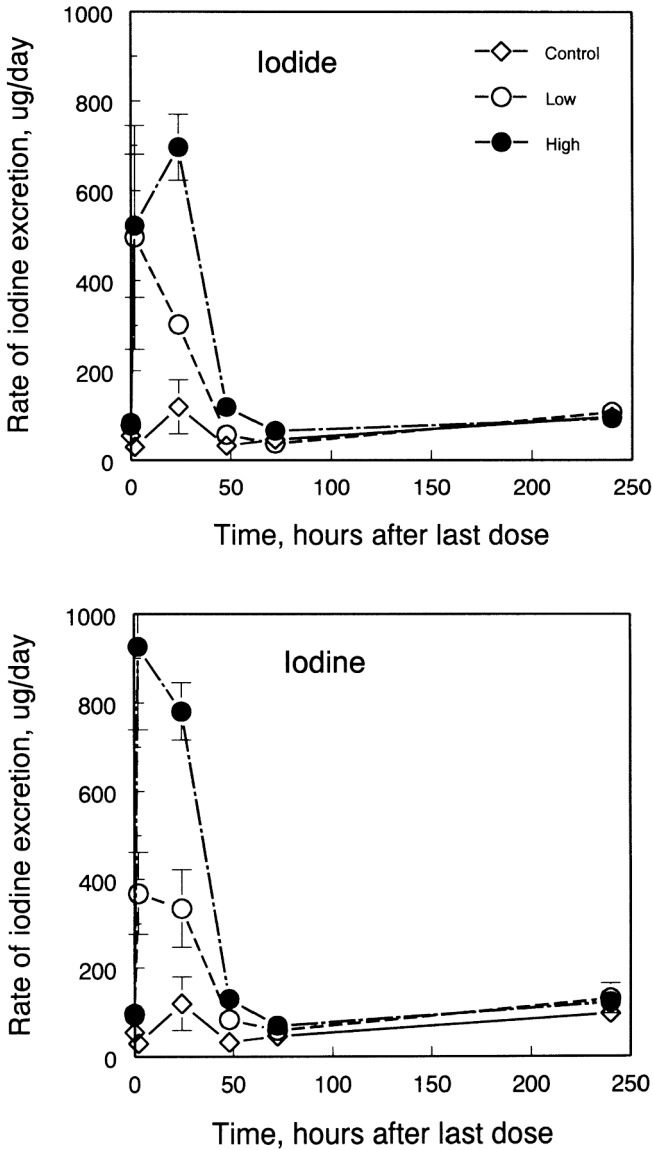


FIGURE 5. Urinary excretion of iodine (\pm SEM) at baseline and 2, 24, 48, 72, and 240 h after final low dose (0.3 mg/kg body weight) or high dose (1.0 mg/kg body weight) of iodide (top panel) or iodine (bottom panel), as compared to control group.

human gastrointestinal tract for this phenomenon to have a substantive impact on thyroid hormone levels in humans.

These results are consistent with results observed by administration of other forms of iodine. Georgitis et al. (1993) used a dosing schedule of 32 mg free iodine (as tetraglycine) for 7 d, and Namba et al. (1993) provided

27 mg/d of iodide for a period of 14 d. Both studies documented small declines in T₄ and elevations of TSH. Our low dose provided 20–30 mg/d and the high dose as much as 70 mg/d for a similar period. Paul et al. (1988) studied the effects of iodide at doses of 0.25, 0.5, and 1.5 mg/d for 14 d. Small but significant depressions in T₄ and T₃ were observed along with a small increase in TSH at 1.5 mg/d. No effect was observed at the lower doses. Therefore, some concern must be expressed over the chronic use of iodine as a disinfectant of drinking water. Effective concentrations of free iodine required for disinfection of water would give rise to doses of iodine as high as 2–5 mg/d. Shorter term exposures are unlikely to present a problem as the excess iodine appears to be rapidly eliminated. The recovery of the iodide dose in the urine at high concentrations was not as great as for iodine. This may have resulted from a larger role for elimination in perspiration at this high dose. Suzuki and Tamura (1985) found that significant amounts of iodine were eliminated in this manner, particularly in individuals that were physically active.

The minor variations in plasma T₄ and T₃ levels observed in the present study are not the primary concern for long-term adverse health effects in themselves. Problems are more likely to be associated with consistently elevated plasma TSH concentrations. This could have more serious long-term impacts on health that might be considered more fully in future studies. Health concerns that might arise from these effects would include goiter, and increased risk from cancer of the thyroid (Williams et al., 1977; Hill et al., 1989; Edmonds & Tellez, 1988), but there may also be other less well defined alterations in the function of other endocrine organs (Thomas et al., 1979).

In summary, the present experiment in humans failed to confirm the differential effect of I₂ on maintenance of serum T₄ concentrations relative to the effects of I⁻ that was observed in prior experiments in rats. The reaction of I₂ with metabolites of thyroid hormones in the intestine that appears responsible for this effect in rats probably also exists at some level in humans. The concentrations of such metabolites in the human intestinal tract may be too low for their iodination to significantly affect circulating concentrations of T₄. Based on the elevations in TSH seen in the present and prior studies, there should be some concern over the potential impacts of chronic consumption of iodine in drinking water.

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