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Effects of Six Months of Daily Low-Dose Perchlorate Exposure on Thyroid Function in Healthy Volunteers

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Context: Perchlorate has been detected in U.S. drinking water supplies at levels ranging from 4 to 200 μg/liter as well as in agricultural products. Perchlorate is known to be a competitive inhibitor of iodine uptake by the thyroid through the sodium-iodide symporter.

Objective: The objective of the study was to determine whether prolonged exposure (6 months) to low levels of perchlorate would perturb thyroid function.

Design: This was a prospective, double-blinded, randomized trial.

Participants: The study population consisted of 13 healthy volunteers.

Intervention: Interventions included placebo *vs.* 0.5 mg or 3.0 mg potassium perchlorate daily.

Main Outcome Measures: Serum thyroid function tests, 24-h radioactive iodine uptake, serum thyroglobulin (Tg), urinary iodine and perchlorate, and serum perchlorate were measured.

Results: Mean urinary perchlorate value during ingestion of 0.5 mg perchlorate daily was 332.7 $\pm$ 66.1 μg per 24 h or 248.5 $\pm$ 64.5 μg/g creatinine and mean values for the four subjects who received 3 mg perchlorate daily were 2079.5 $\pm$ 430.0 μg per 24 h or 1941.7 $\pm$ 138.5 μg/g creatinine. There was no significant change in the thyroid ^{123}I uptakes during perchlorate administration. There were no significant changes in serum T_3, free T_4 index, TSH, or Tg concentrations during the exposure period, compared to baseline or postexposure values. Urine iodine values for the 3-mg perchlorate group were higher, but not significantly so, at baseline than during perchlorate exposure.

Conclusions: We observed that a 6-month exposure to perchlorate at doses up to 3 mg/d had no effect on thyroid function, including inhibition of thyroid iodide uptake as well as serum levels of thyroid hormones, TSH, and Tg. (***J Clin Endocrinol Metab* 91: 2721–2724, 2006**)

PERCHLORATE SALTS HAVE been used as pharmaceuticals and oxidizers in solid propellants for rockets and missiles and in explosives, fireworks, and road flares and air bag inflation systems (1). Since 1997, perchlorate has been found in drinking water throughout the United States at levels ranging from 4 to 200 μg/liter and in lettuce and milk (2). Environmental perchlorate contamination has been attributed to industries that manufacture and use perchlorate. However, detection of low perchlorate levels at locations far from such sources suggests that perchlorate may come from natural processes and Chilean nitrate fertilizers (3).

Perchlorate is a competitive inhibitor of thyroid iodine uptake through the sodium-iodide symporter (4). Prolonged major inhibition of iodide uptake can result in decreased synthesis of thyroid hormones. The ability of perchlorate to inhibit iodine uptake was the basis for its use in the 1950s and 1960s to treat hyperthyroidism (5), but after a few reported cases of fatal aplastic anemia in patients treated with high doses (600–1600 mg/d), use of perchlorate essentially ceased. However, more recent experience using perchlorate to treat Graves' disease and iodine-induced hyperthyroidism demonstrated no serious side effects at doses less than 1000 mg/d for up to 1 yr (6, 7).

In view of the reported environmental perchlorate contamination (2, 3), the potential health effects from this relatively low-level perchlorate ingestion are a matter of public health interest. There have been several recent human studies regarding the health effects of perchlorate. U.S. studies have not shown any thyroid effects at drinking water perchlorate concentrations of 4–16 μg/liter (8, 9). Observational studies in the Atacama region of Chile, where drinking water perchlorate concentrations are up to 100–120 μg/liter, have also not shown any effect of perchlorate on the thyroid in newborns, school-aged children, or pregnant women (10). In a recent study from an area in Israel where well water perchlorate contamination is more than 300 μg/liter, newborn serum T_4 values were normal (11).

Only one ecological drinking water study in the United States has reported thyroidal effects. TSH levels were elevated in newborns in Yuma City, Arizona, where the drinking water perchlorate concentration was 6 μg/liter, compared with newborns in Flagstaff, Arizona, where perchlorate is undetectable in the water supply (12). However, the demographics and altitudes of the two towns are

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Abbreviations: FTI, Free T_4 index; RAIU, thyroid ^{123}I uptake; Tg, thyroglobulin.

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different. When newborns from Yuma City were compared with those from an adjacent town in which perchlorate is not found in the drinking water, serum TSH values were normal and similar (13).

Studies in perchlorate production workers exposed to perchlorate via inhalation at doses up to 34 mg/d for a mean of 3 yr have not indicated any adverse effects on thyroid structure or serum TSH, thyroid hormones, or thyroglobulin (Tg) concentrations (14, 15) even though 14-h thyroid ^{123}I uptakes (RAIU) were decreased by an average of 38% after three consecutive 12-h shifts as compared with preshift RAIU.

Several controlled studies in normal volunteers have evaluated thyroid effects of 14-d exposures to perchlorate in drinking water (16–18). The thyroid RAIUs significantly decreased by 38% in healthy volunteers consuming 10 mg perchlorate daily. There were no significant changes in serum thyroid hormone or TSH concentrations during perchlorate administration. Administration of 3 mg perchlorate daily for 14 d resulted in an insignificant 10% decrease in the 24-h RAIU (17). A perchlorate pharmacokinetic study was reported in which volunteers drank water for 14 d containing perchlorate (~0.5, 1.4, 7, and 35 mg/d for a 70-kg individual) (18). On d 14, 24-h RAIUs for the 0.5 mg/d exposure group were not significantly different from baseline, whereas 24-h RAIUs at the other three doses had decreased significantly by 16, 45, and 67% from baseline, respectively.

Although the human drinking water and occupational studies provide some evidence that low-level perchlorate exposure does not adversely affect the thyroid, exposure was for only 2 wk in the short-term studies, and in the worker studies, the exposures were not continuous. The aim of the present study was to determine whether more prolonged exposure (6 months) to low perchlorate levels would perturb thyroid function.

Subjects and Methods

Experimental subjects

The protocol was approved by the Institutional Review Boards at Loma Linda University School of Medicine, the Jerry L. Pettis Memorial Veterans Administration Medical Center, and Boston University School of Medicine.

Subjects were recruited by direct mail advertising in the Loma Linda and San Bernardino, California, area. Subjects with a known history of thyroid disease or taking thyroid hormone or antithyroid medications were excluded. During the first year, 94 subjects provided informed consent, with 24 subjects eventually being randomized to study medication. Of the original 94 subjects, 15 declined further screening evaluation, and 55 were excluded due to an abnormal baseline laboratory test or preexisting illness. Of the original 24 randomized subjects, 14 completed the 7-month study. The 10 randomized subjects who did not complete the study withdrew due to personal scheduling conflicts. None of the 24 randomized study subjects developed an abnormal laboratory or clinical finding or a study-related adverse event. Of the 14 subjects (aged 25–65 yr) completing the study, nine were women, 12 were Caucasian, and two were African-American. Further volunteers could not be recruited due to adverse publicity (Environmental Working Group; www.ewg.org/reports/perchlorate/pr.html/).

Preparation of capsules

Longwood Pharmaceutical Research, Inc. at the Massachusetts College of Pharmacy and Allied Sciences (Boston MA), prepared perchlorate (reagent grade potassium perchlorate) and placebo capsules using good manufacturing practices as specified by the U.S. Food and Drug Administration. Capsules were checked every 3 months for stability.

Protocol

The 14 subjects were randomly and blindly assigned to four dose groups: placebo or 0.5, 1.0, or 3.0 mg perchlorate, taking the dose daily between 0700 and 1000 h for 6 months. Assuming an average daily water ingestion of 2 liters, the 3.0-mg dose corresponds to approximately 1500 μg/liter perchlorate and the 0.5-mg dose to 250 μg/liter. Physical examination by one of the investigators (A.F.), including palpation of the thyroid, was done monthly during the 7 months of study. Blood (~2 h after capsule ingestion) and 24-h urines were obtained at baseline and monthly during perchlorate or placebo administration and 1 month later. Serum thyroid function tests and perchlorate and urine iodine, perchlorate, and creatinine were measured monthly. Capsule counts were monitored monthly. Twenty-four-hour thyroid RAIU and serum Tg and Tg antibodies were measured at baseline, 3 and 6 months during perchlorate or placebo ingestion, and 1 month after study medication had been discontinued. To be certain that perchlorate was not adversely affecting serum TSH and free T_4 index (FTI) concentrations, complete blood counts, or blood chemistries during the study, these parameters were assessed monthly.

Laboratory tests

Serum perchlorate measurement was carried out using HPLC at Boston Medical Center as described earlier (14). The perchlorate content of the 24-h urine samples was measured at the Centers for Disease Control and Prevention Laboratories (Atlanta, GA) using ion chromatography-mass spectrometry (19). Serum total T_3, T_4, FTI, and TSH concentrations were measured at the end of the study in the same assay at the Boston Medical Center Clinical Chemistry laboratories by chemiluminescence using the Bayer Advia Centaur automated system (Bayer Healthcare, Tarrytown, NY). Serum Tg and Tg antibodies were measured using chemiluminescence on the Nichols Advantage (Nichols Institute Diagnostics, San Juan Capistrano, CA). Urinary iodine was measured using the Sandell-Kolthoff reaction. Complete blood counts and serum chemistries were carried out in the Jerry L. Pettis Memorial Veterans Administration Medical Center assay laboratory. The 24-h thyroid RAIU was measured at the Loma Linda University School of Medicine Department of Nuclear Medicine (Loma Linda, CA). Subjects were given 100 μCi ^{123}I orally approximately 2 h after the morning ingestion of the perchlorate capsule. They returned to the laboratory 24 h later for measurement of the thyroid ^{123}I uptake.

Statistical analysis

Values are reported as the mean ± SD and significant differences as $P < 0.05$. Statistical analyses were carried out using SAS (version 8; SAS Institute, Cary, NC). Baseline differences in mean values by group were assessed using ANOVA. Changes over time by treatment group were assessed using repeated-measures ANOVA.

Results

Because only one subject received 1 mg perchlorate daily, this subject was omitted from the analysis. No subjects developed abnormal serum TSH or FTI values during the study.

Urine perchlorate (Table 1)

Urine perchlorate was detected at low levels at baseline in all 13 subjects averaging 9.2 ± 5.7 μg per 24 h or 7.3 ± 5.5 μg/g creatinine. It remained low in the four subjects receiving placebo. In the five subjects given 0.5 mg perchlorate daily, perchlorate values over the 6 months rose appropriately (332.7 ± 66.1 μg per 24 h or 248.5 ± 64.5 μg/g creatinine), as did mean values in the four subjects who received 3 mg perchlorate daily (2079.5 ± 430.0 μg per 24 h or

TABLE 1. The effect of perchlorate ingestion on serum and urine perchlorate and urine iodine values

	Placebo (n = 4; mean ± SD)	0.5 mg Perchlorate (n = 5; mean ± SD)	3.0 mg Perchlorate (n = 4; mean ± SD)
Urine iodine (μg/total volume)			
Before	300 ± 181.3	257.8 ± 119.4	311.5 ± 263.2
During	264.2 ± 78.4	294.9 ± 78.1	238.2 ± 132.7
After	238 ± 62.8	238.2 ± 132.7	188.4 ± 95
Urine iodine (μg/g creatinine)			
Before	194.9 ± 87	184 ± 81.2	322 ± 357
During	245.7 ± 106.4	206.2 ± 48.2	214.7 ± 106.6
After	197 ± 59.2	256.9 ± 152.2	192.8 ± 110.1
Urine CLO4 (μg/total volume)[a]			
Before	7.3 ± 1.0	11.9 ± 8.1	7.3 ± 3.1
During	9.2 ± 5.0	332.7 ± 66.1	2079.5 ± 430
After	7.1 ± 3.4	9.4 ± 4.3	10.1 ± 6.6
Urine CLO4 (μg/g creatinine)			
Before	5.4 ± 1.7	9.1 ± 7.7	7.4 ± 4.5
During	8.2 ± 5.0	248.5 ± 64.5	1941.7 ± 138.5
After	5.2 ± 1.8	8.2 ± 5.0	10.4 ± 7.2
Serum CLO4 (μg/liter)[b]			
Before	0	0	0
During	0	24.5 ± 16	77.9 ± 18.2
After	0	0	0

There were no significant differences in perchlorate and iodine values between groups at baseline.
[a] The minimum detection level for perchlorate was 0.025 μg/liter in urine.
[b] The minimum detection level for perchlorate was 1.0 μg/liter in serum.

1941.7 ± 138.5 μg/g creatinine). Thus, about 65–70% of the daily dose was excreted over a 24-h period.

Serum perchlorate (Table 1)

Perchlorate was not detected in baseline samples or in those subjects receiving placebo. Serum perchlorate was detected in subjects receiving perchlorate, averaging over the 6 months 24.5 ± 16 μg/liter in the 0.5-mg perchlorate group and 77.9 ± 18.2 μg/liter in the 3-mg group. Perchlorate was not detected in any sera 1 month after perchlorate was discontinued.

Urine iodine (Table 1)

Because subjects were not on a controlled diet, daily urine iodine values varied throughout the study, ranging from 54 to 840 μg/g creatinine (median 174 μg/g creatinine). Urine iodine values for the 3-mg perchlorate group were higher, but not significantly so, at baseline than during perchlorate exposure (322 ± 357 *vs.* 214.7 ± 106 μg/g creatinine or 311.5 ± 263.2 *vs.* 238.2 ± 132.7 μg per 24 h).

Thyroid RAIU (Table 2)

The thyroid RAIU was measured at baseline, 3 and 6 months during perchlorate or placebo ingestion, and 1 month later. There was no significant change in the thyroid RAIU during perchlorate administration.

Thyroid function tests (Table 2)

There were no significant changes in serum total T_3, FTI, TSH, or Tg concentrations during the exposure period, compared with values before and after perchlorate exposure. Tg antibodies were not detected in any subject.

Discussion

Although urinary iodine levels were variable both among subjects and across time, there was no relationship between urinary iodine levels and perchlorate levels in serum or urine. Iodine levels were comparable with those of the general population, with the median urinary iodine (174 μg/g

TABLE 2. The effect of perchlorate ingestion for 6 months on thyroid function tests

	Placebo (n = 4; mean ± SD)	0.5 mg Perchlorate (n = 5; mean ± SD)	3.0 mg Perchlorate (n = 4; mean ± SD)
TSH (μIU/ml)			
Before	1.1 ± 0.5	1.6 ± 0.7	2.2 ± 0.6
During	1.1 ± 0.4	1.5 ± 0.6	2.2 ± 0.9
After	1.2 ± 0.5	1.6 ± 0.5	2.6 ± 1.8
FTI			
Before	2.8 ± 0.2	2.5 ± 0.4	2.3 ± 0.1
During	2.6 ± 0.2	2.4 ± 0.4	2.3 ± 0.3
After	2.3 ± 0.2	2.4 ± 0.2	2.4 ± 0.3
T_3 (ng/dl)			
Before	181.9 ± 39.1	160.7 ± 41.3	119.6 ± 24.0
During	179.4 ± 51.1	160.0 ± 39.7	118.0 ± 26.4
After	162.3 ± 34.8	163.5 ± 44.9	115.2 ± 16.5
Tg (ng/ml)			
Before	19.8 ± 14.0	23.7 ± 8.5	36.9 ± 32.9
During	20.3 ± 13.7	24.5 ± 4.2	41.7 ± 35.6
After	19.0 ± 12.8	25.0 ± 8.5	44.5 ± 42.7
24-h RAIU			
Before	17.7 ± 4.9	15.6 ± 1.6	19.6 ± 4.9
During	15.8 ± 3.8	14.1 ± 4.4	19.8 ± 5.7
After	17.6 ± 2.4	16.6 ± 3.3	22.5 ± 6.1

There were no significant differences in TSH, FTI, T_3, Tg, or 24-h RAIU values between groups at baseline. Normal ranges: TSH, 0.35–5.5 μIU/ml; FTI, 1–4; T_3, 60–181 ng/dl; and Tg, 4–40 ng/ml. Intraassay coefficients of variation are: T_4, < 3.2%; T_3 uptake < 3.2%; T_3 < 3.2%; and TSH < 2.5%. For T_3, the conversion factor to go from conventional to SI units is 0.0154.

creatinine) corresponding to approximately the 70th percentile value in the general population (20).

We observed that a 6-month exposure to perchlorate at 0.5 and 3 mg/d had no effect on thyroid function, including inhibition of thyroid ^{123}I uptake and serum levels of thyroid hormones, TSH, and Tg. These results are similar to those of Lawrence *et al.* (17) in a 14-d study but differ somewhat from those of Greer *et al.* (18), who observed a significant 16% decrease in RAIU after a 14-d exposure of 1.4 mg perchlorate daily for a 70-kg individual. The difference between our long-term results and those from the short-term studies may be due to the small number of subjects in our study, differences in the dosing regimen (once daily *vs.* semicontinuous), or up-regulation of the sodium-iodide symporter as an adaptive response in the long-term study (21).

This is the first study to provide information regarding potential thyroid effects of continuous, long-term exposure to defined low levels of perchlorate. Although perchlorate plant workers were exposed to high amounts of perchlorate on a long-term basis, the exposure pattern in those studies involved 3 d of exposure followed by 3 d without exposure. The intermittent exposure pattern may allow the thyroid to recover, at least partially, from any perchlorate-induced inhibition of iodide uptake during the 3 nonexposed days, thus potentially dampening effects that might be observed with continuous exposure.

This study was limited by the small sample size and is obviously underpowered. Unfortunately, further such studies cannot be carried out at present in the United States. In addition, the once-per-day dosing regimen does not reflect how actual exposures via drinking water and food consumption would occur. Nonetheless, the results suggest that healthy, euthyroid individuals, with normal levels of iodine intake, can tolerate chronic exposure to perchlorate at doses up to 3 mg/d without any effects on thyroid function, including inhibition of iodide uptake.

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