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EFFECTS OF LOW DOSE ORAL IODIDE SUPPLEMENTATION ON THYROID FUNCTION IN NORMAL MEN

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SUMMARY

Previous studies have demonstrated that short-term oral iodide administration, in doses ranging from 1500 μg to 250 mg/day, has an inhibitory effect on thyroid hormone secretion in normal men. As iodide intake in the USA may be as high as 800 μg/d, we investigated the effects of very low dose iodide supplementation on thyroid function. Thirty normal men aged 22–40 years were randomly assigned to receive 500, 1500, and 4500 μg iodide/day for 2 weeks. Blood was obtained on days 1 and 15 for measurement of serum T4, T3, T3-charcoal uptake, TSH, protein-bound iodide (PBI) and total iodide, and 24 h urine samples were collected on these days for measurement of urinary iodide excretion. TRH tests were performed before and at the end of the period of iodide administration. Serum inorganic iodide was calculated by subtracting the PBI from the serum total iodide. We found significant dose-related increases in serum total and inorganic iodide concentrations, as well as urinary iodide excretion. The mean serum T4 concentration and free T4 index values decreased significantly at the 1500 μg/day and 4500 μg/day doses. No changes in T3-charcoal uptake or serum T3 concentration occurred at any dose. Administration of 500 μg iodide/day resulted in a significant increase ($P < 0{\cdot}005$) in the serum TSH response to TRH, and the two larger iodide doses resulted in increases in both basal and TRH-stimulated serum TSH concentrations. Thus, iodide supplementation within the range of normal daily intake in the USA has a significant inhibitory effect on thyroid hormone secretion in normal men.

The synthesis of normal quantities of thyroid hormone requires an adequate dietary iodide intake, but iodide intake in excess of that needed for normal thyroid function may have inhibitory effects on thyroid function. These anti-thyroid effects of iodide are mediated via two mechanisms: inhibition of iodide organification, resulting in decreased thyroid hormone synthesis, and inhibition of thyroglobulin proteolysis, resulting in decreased thyroid hormone secretion (Utiger, 1972).

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Administration of pharmacological doses of iodide to susceptible individuals may result in hypothyroidism. Patients with Hashimoto's disease and those who have previously received radioactive iodine therapy for Graves' disease appear to be particularly susceptible (Braverman *et al.*, 1969; Braverman *et al.*, 1971). In most normal individuals, however, acute and chronic iodide administration rarely results in clinically significant thyroid dysfunction.

Subtle changes in thyroid function, however, have been demonstrated in normal subjects receiving 50–250 mg iodide/day for 10–14 days. The changes consist of small but significant decreases in serum T4 and T3 concentrations along with small, compensatory increases in basal serum TSH concentrations and exaggerated serum TSH responses to TRH (Vagenakis *et al.*, 1973; Saberi & Utiger, 1975). A more recent study demonstrated that iodide supplementation of 1500 μg/day has a significant inhibitory effect on thyroid function in normal men (Meyers *et al.*, 1985). To define more clearly the effects of low-dose iodide supplementation, in amounts approaching the normal daily iodide intake in the USA, we studied the effects of 500–4500 μg iodide/day for 14 days on thyroid function in normal men.

MATERIALS AND METHODS

Subjects and study protocol

Thirty normal men between the ages of 22 and 40 years (mean age 27) were randomly assigned to receive 500, 1500 or 4500 μg iodide/day. All studies were performed on the Clinical Research Center (CRC) of the Medical College of Virginia. The study was approved by the Virginia Commonwealth University Committee on the Conduct of Human Research, and each man gave informed written consent.

On Day 1 of the study, the men were admitted to the CRC at 0800 h, after an 8-h fast. All had collected a 24 h urine specimen for iodide and creatinine measurements during the day prior to admission. Baseline studies included serum T4, T3, T3-charcoal uptake, TSH, protein-bound iodide (PBI) and total iodide determinations. All then received an i.v. bolus dose of 500 μg. TRH, and blood samples were collected at 15 min intervals for 1 h for TSH determinations. After completion of the TRH test, the men received their initial dose of iodide. The iodide solutions were prepared by dissolving sodium iodide, in deionized water, and adjusting the concentrations to 500, 1500 or 4500 μl/ml. Ascorbic acid (1 mg/ml) was added to each solution. The men took the iodide in 0·5 ml aliquots, twice daily, for 14 days. On day 15, the protocol outlined for day 1 was repeated, completing the study. Subjects were instructed to continue their usual diets throughout the study period. No man reported any adverse effects during the 2 week period of iodide administration. In addition, no significant weight changes or symptoms of thyroid dysfunction were detected.

Assays

Urinary and serum total iodide, urinary creatinine and serum PBI were measured by Smith Kline Bio-Science Laboratories, Van Nuys, CA. Serum inorganic iodide was calculated by subtracting the serum PBI from the serum total iodide. Serum T4, T3 and TSH concentrations and T3-charcoal uptake ratios were measured in duplicate by

Table 1. Urinary iodide excretion and serum iodide concentrations before and after iodide administration

Iodide dose	Urinary iodide (μg/24 h)	Total iodide (μg/dl)	Serum PBI (μg/dl)	Inorganic iodide (μg/dl)
500 μg/d				
Day 1	256±44	6·2±0·3	5·0±0·3	1·2±0·1
Day 15	638±58*	6·7±0·3	4·8±0·2	1·9±0·3*
1500 μg/d				
Day 1	285±49	6·3±0·3	5·0±0·3	1·3±0·2
Day 15	1498±105*	7·7±0·2*	4·7±0·2	3·0±0·2*
4500 μg/d				
Day 1	319±51	6·0±0·3	4·7±0·3	1·3±0·2
Day 15	5035±315*	12·7±1·2*	4·8±0·3	7·9±0·9*

Mean±SEM.
* $P<0·001$, compared with day 1.

previously described methods (Chopra, 1972; Lieblich & Utiger, 1972; Utiger, 1979; Bermudez *et al.*, 1975; Uhrmann *et al.*, 1978). The serum free thyroxine index (FTI) was calculated by multiplying the serum T4 concentration by the T3-charcoal uptake ratio. Normal ranges for adults are as follows: T4, 4·5–12·0 μg/dl (58–154 nmol/l); T3 80–180 ng/dl (1·2–2·8 nmol/l); T3-charcoal uptake ratio, 0·85–1·15; and TSH $<1·0$–5·0 uU/ml ($<1·0$–5·0 mU/l). For urine and serum iodide measurements, 1 μg iodide = 7·9 nmol iodide. All samples from an individual man were analysed in the same assay.

Data analysis

Paired Student's *t*-tests were used to compare within-group changes before and after iodide administration. The results are expressed as the mean±SEM.

RESULTS

The changes in serum and urinary iodide resulting from the three different doses of iodide are shown in Table 1. The significant dose-related increases in urinary iodide excretion were proportionate to the iodide dose administered, confirming compliance with the prescribed regimen. Similar changes occurred in serum total iodide and inorganic iodide concentrations. None of the iodide doses caused significant changes in mean serum PBI concentrations.

The effects of iodide on circulating iodothyronine concentrations and the T3-charcoal uptake values are shown in Table 2. There were no significant changes in the men who received 500 μg iodide/day. However, administration of 1500 and 4500 μg/day resulted in significant decreases in mean serum T4 concentrations and free T4 index values. Serum T3 concentrations and T3-charcoal uptake ratios did not change at any of the iodide doses.

The changes in basal and TRH-stimulated TSH concentrations are shown in Table 3. The mean basal serum TSH concentration increased in the men who received 1500 and 4500 μg iodide/day, but not in those who received 500 μg. However, a significant enhancement of the TSH response to TRH occurred in all three groups.

Table 2. Serum thyroid hormone concentrations before and after iodide administration

Iodide dose	Serum T4 (μg/dl)	T3-charcoal uptake ratio	FT4I	Serum T3 (ng/dl)
500 μg/day				
Day 1	9·2±0·5	1·06±0·04	9·8±0·8	153±8
Day 15	9·2±0·4	1·09±0·04	10·0±0·6	158±7
P value*	NS†	NS	NS	NS
1500 μg/day				
Day 1	8·6±0·4	1·02±0·04	8·7±0·5	162±11
Day 15	7·5±0·9	1·00±0·05	7·5±0·4	161±7
P value	0·005	NS	0·005	NS
4500 μg/day				
Day 1	8·9±0·6	1·12±0·09	9·9±0·6	151±9
Day 15	8·2±0·7	1·11±0·04	9·0±0·6	155±6
P value	0·02	NS	0·005	NS

Mean±SEM.
FT4I = Free thyroxine index.
* *P* value, Day 15 compared with day 1.
† NS, not significant.

Table 3. Effect of iodide on basal and TRH-stimulated serum TSH concentrations

	TSH (μU/ml) min after TRH					Maximum TSH increment
Iodide dose	0	15	30	45	60	
500 μg/day						
Day 1	3·0±0·3	9·7±1·4	12·0±1·8	11·0±1·7	9·7±1·8	9·0±1·6
Day 15	3·3±0·5	11·1±1·5	15·2±4·8	13·7±2·3	12·8±2·3	12·5±2·2
P value*	NS†	0·05	0·02	0·02	0·002	0·003
1500 μg/day						
Day 1	2·5±0·3	9·6±1·5	11·6±1·8	10·7±1·7	8·7±1·5	9·4±1·7
Day 15	3·7±0·5	14·2±2·2	16·3±2·2	14·6±1·9	12·5±1·9	12·8±2·0
P value	0·04	0·004	0·002	0·01	0·002	0·005
4500 μg/day						
Day 1	2·1±0·4	8·8±1·1	9·5±1·1	8·9±1·0	7·8±0·9	7·5±1·0
Day 15	3·7±0·6	12·7±1·8	15·5±2·0	14·0±1·4	12·0±1·6	12·2±1·6
P value	0·008	0·003	0·001	0·001	0·001	0·001

Mean±SEM.
* *P* value, day 15 compared with day 1.
† NS, not significant.

DISCUSSION

Previous studies have demonstrated that pharmacological doses of iodide, ranging from 10 to 1000 mg/day for 2–11 weeks, result in significant decreases in serum T4 and free T4 concentrations, and compensatory increases in serum TSH concentrations (Vagenakis *et al.*, 1973; Saberi & Utiger, 1975; Ikeda & Nakataki, 1976; Jubiz *et al.*, 1977). However, the effects of iodide supplementation in the range of current daily intake levels, below 1000 μg/day, on thyroid function in normal subjects is not known.

Interest in the effects of low doses of iodide derives from recent studies demonstrating that the addition of only 1000–1500 μg iodide to the normal dietary intake had significant anti-thyroid effects. We previously reported that the administration of 200 mg/day erythrosine (2′,4′,5′,7′-tetraiodofluorescein, FD&C Red No. 3), a widely used food colouring, to normal subjects for 2 weeks resulted in changes in thyroid function similar to those associated with daily iodide administration of 50–250 mg (Gardner *et al.*, 1987). The daily iodide load associated with the ingestion of 200 mg erythrosine/d was approximately 1000 μg. Subsequent studies confirmed that oral iodide supplementation of 1500 μg/day resulted in subtle but significant decreases in serum T4 and T3 concentrations and compensatory increases in TSH secretion, changes identical to those occurring with much higher doses of iodide (Meyers *et al.*, 1985). In all of the above studies, serum iodothyronine and TSH concentrations remained within the normal range during iodide administration.

Direct assessments of daily iodide intake in the USA, based on urinary iodide excretion, are not currently available. However, indirect estimates based on 'market basket' surveys suggest the normal daily intake is as high as 700–800 μg/day, with some regional variability (Park *et al.*, 1981). In this study, we examined the effects of iodide supplementation above and below this intake level in an attempt to establish a 'no-effect' level of acute iodide administration in normal men, and to verify previous studies using 1500 μg iodide/day. The 500 μg/day iodide dose resulted in a mean urinary iodide excretion that would be considered normal in the USA, 638 μg/24 h. This dose did not produce any significant changes in serum T4, T3 or basal serum TSH concentrations. It did, however, result in a small but significant ($P < 0{\cdot}005$) enhancement of the serum TSH response to TRH, indicating a definite anti-thyroid effect of this low dose of iodide. Higher iodide doses, 1500 and 4500 μg/day, produced significant decreases in mean serum T4 concentration and free thyroxine index values, and enhancement of both basal and TRH-stimulated TSH secretion. No significant changes in serum T3 concentrations occurred at any dose of iodide.

While numerous studies have now documented significant anti-thyroid effects of acute iodide administration, extrapolation of these data to chronic iodide exposure is difficult. Particular sensitivity to the anti-thyroid effects of iodide has been demonstrated in patients with Hashimoto's thyroiditis, patients with Graves' disease after either surgical or radioactive iodine therapy, and patients receiving lithium carbonate (Shopsin *et al.*, 1973). Normal individuals, however, appear to be resistant to chronic iodide exposure in terms of development of either goitre or clinically significant hypothyroidism, although chronic exposure to extremely high doses of iodide, greater than 100 mg/day, may result in goitre and hypothyroidism (Suzuki *et al.*, 1965; Jubiz *et al.*, 1977). It is unlikely that chronic exposure to the doses of iodide used in this study would have significant clinical

consequences. A recent study demonstrated that administration of 1500 μg iodide/day for 12 weeks to normal subjects and patients with Hashimoto's thyroiditis had little effect on circulating iodothyronine concentrations (Paul *et al.*, 1987). However, small increases in basal serum TSH concentrations, similar to those we found, occurred.

In summary, short-term iodide supplementation, within the range of normal daily intake in many parts of the world, has small but significant anti-thyroid effects in normal men. The consequences of prolonged exposure to this level of iodide and the 'no-effect' level of iodide supplementation remain to be determined.

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