

□ CASE REPORT □

Povidone Iodine-induced Overt Hypothyroidism in a Patient with Prolonged Habitual Gargling: Urinary Excretion of Iodine after Gargling in Normal Subjects

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Abstract

Iodine-induced hypothyroidism that develops in patients who gargle routinely with povidone iodine is well known. Usually the hypothyroidism is mild and resolves spontaneously upon cessation of gargling. Here, we report a 63-year-old patient with overt hypothyroidism that developed due to habitual gargling with povidone iodine for more than 10 years. The urinary excretion of iodine was estimated to be greater than 5 mg/day, based on values obtained from 18 normal subjects who gargled three times a day (4.6 ± 2.1 mg, mean \pm SD). After discontinuation of the gargling, the patient has been euthyroid for more than 10 months.

Key words: povidone-iodine, hypothyroidism, iodine-induced hypothyroidism, urinary excretion of iodine

(DOI: 10.2169/internalmedicine.46.1899)

Introduction

Povidone-iodine (poly[(2-oxopyrrolidin-1-yl)ethylene] iodine) (Isodine Gargle Meiji Seika Kaisha, Ltd., Tokyo, Japan) is a widely used gargling preparation in Japan.

Since it contains 7 mg iodine per ml, a significant proportion of the iodine is absorbed or swallowed during or after gargling. Although a daily single mouthwash with 5% povidone iodine for 15-30 seconds for 6-24 weeks reportedly does not affect thyroid function in euthyroid patients with gingivitis (1), iodine-induced hypothyroidism may develop in certain patients susceptible to iodine (2). Usually, the hypothyroidism is mild, and resolves spontaneously upon cessation of gargling. However, a few patients develop moderate to severe hypothyroidism if they continue to gargle with povidone iodine for a prolonged period (3), although the amount of iodine swallowed and excreted into urine has not been reported. Since the package insert carries only a brief warning that the agent should not be used by individuals with hypersensitivity to iodine, and should be used with care in individuals with thyroid dysfunction (4), povidone iodine gargling is frequently prescribed by general physicians and

otolaryngologists for patients with various oral or pharyngeal complaints. Here, we report a patient with overt hypothyroidism that developed due to habitual gargling with povidone iodine for more than 10 years. Since this was a relatively severe case, another case of subclinical povidone iodine-induced hypothyroidism, which is occasionally encountered by general physicians, is also presented.

Furthermore, since no data are available on the amount of iodine swallowed and excreted into urine by gargling with povidone iodine (5), the urinary excretion of iodine was studied in 20 normal subjects who were asked to gargle three times a day, in accordance with the instructions supplied in the package insert.

Case Report

Patient 1

A 63-year-old male patient was admitted in late August 2005 to the Institute of Gastroenterology, Tokyo Women's Medical University (TWMU) Hospital, with the chief complaints of general malaise, anorexia, weight loss, diarrhea, and constipation of 2 months duration. The patient had de-

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Received for publication June 26, 2006; Accepted for publication November 25, 2006

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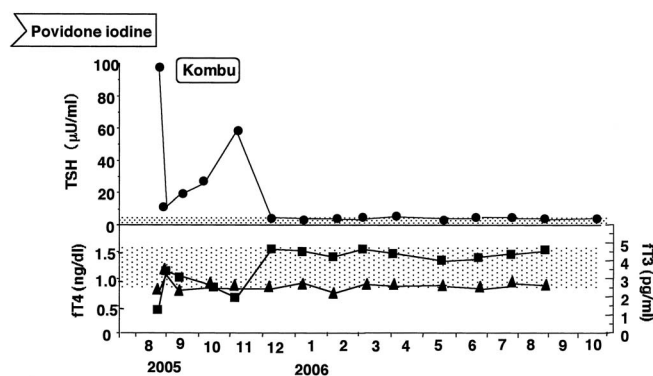


Figure 1. Clinical course of a patient with iodine-induced hypothyroidism. Upon cessation of gargling with povidone-iodine and taking kombu, the patient (Patient 1) has been euthyroid for the last 10 months. Dotted areas indicate normal ranges of TSH (0.38–4.3 μU/ml) and fT4 (0.94–1.60 ng/dl). ■-■ ; fT4, ▲-▲ ; fT3

veloped mild cerebral infarction in 1985, and in 1988 had developed mitral stenosis with atrial fibrillation and sick sinus syndrome, necessitating insertion of a pacemaker. In 2001, the patient underwent mitral commissurotomy. In 2002, he developed pollakiuria, and visited the Urology Clinic monthly as an outpatient. In 2003, he developed tinea pedis and visited the Dermatology Department of TWMU Hospital monthly as an outpatient. On admission, the patient was taking warfarin 1–2 mg, furosemide 20 mg, spironolactone 25 mg, naftopidil 25 mg, allopurinol 200 mg, terbinafine hydrochloride 125 mg, oxatomide, and *Bifidobacterium* granular powder. Physical examination showed that the patient was 151.2 cm tall and weighed 47.9 kg. His body temperature was 35.9°C, blood pressure 129/70, and pulse rate 62 bpm. His hemoglobin level was 11.9 g/dl, hematocrit 35.5%, and the platelet count $17.8 \times 10^4/\text{mm}^3$. Serum levels of AST (44 U/L), LDH (459 U/L) and CPK (498 U) were elevated, whereas ALT, creatinine, uric acid, BUN were within the normal range. Serum levels of Na (129 mEq/L) and Cl (94 mEq/L) were decreased. Results of gastrointestinal examinations (sonography of the upper abdomen, upper GI fiberoptic, barium enema of the bowel) were normal. On the fifth day of admission, thyroid function tests revealed that the serum levels of free T3 and T4 were decreased to 2.22 pg/ml (reference range; 2.40–4.00 pg/ml) and 0.45 ng/dl (reference range; 0.94–1.60 ng/dl), respectively, accompanied by a markedly elevated level of TSH (96.8 μU/ml; reference range (0.38–4.30 μU/ml) (Fig. 1), and the patient was therefore referred to the outpatient clinic of the Institute of Endocrinology.

The patient seemed depressive and spoke slowly, and his face was myxedematous. Anamnesis revealed that the patient had been aware of pharyngeal discomfort for a long period, and had been prescribed 2 to 3 bottles of povidone iodine gargle solution (30 ml/bottle, Isodin Gargle) per month for more than 10 years. Every time he went home, namely three to five times a day, he had gargled with this preparation,

without rinsing his mouth with water after gargling. However, he had stopping gargling 5 days previously, since his admission. Palpation showed that the thyroid gland was slightly enlarged. Ultrasonographic examination revealed a diffuse goiter with slightly non-homogeneous echogenicity. Color Doppler ultrasonography revealed increased blood flow in the whole thyroid gland (Fig. 2A), suggesting potent stimulation of the TSH receptor by TSH (6). The patient agreed to stop gargling with povidone iodine, but claimed it would be necessary to resume gargling after discharge. Therefore, a non-iodine-containing gargling agent (azulen sulfonate-containing gargle: Hachiazule) (Ono Pharmaceutical Co., Osaka, Japan) was prescribed. The patient was discharged with a diagnosis of irritable colon and iodine-induced hypothyroidism, without any supplementation of thyroid hormones.

Twelve days after the patient had stopping gargling with povidone iodine, his serum levels of free T3 and free T4 increased to 3.14 pg/ml and 1.13 ng/ml, respectively, accompanied by a rapid decrease in the TSH level (11.4 μU/ml). The thyroglobulin level was elevated to 760 ng/ml (reference range <30 ng/ml) and gradually decreased to 76 ng/ml in three months. Antibodies against thyroglobulin, thyroperoxidase (TPOAb), and TSH receptor (TRAb) were all negative.

In November, the serum TSH level again increased to 57.6 μU/ml. The patient denied gargling with povidone iodine but had been taking an excessive amount of seaweed, particularly kelp (kombu), in the belief that the iodine it contained was beneficial to his health. The pathophysiology of iodine-induced hypothyroidism was again explained to the patient, and he agreed to take usual Japanese-style meals. In December, the TSH level decreased to the normal range, accompanied by decreased blood flow in the thyroid gland (Fig. 2B). Since then, the patient has remained euthyroid. In October 2006, serum levels of total T4, T3, and TSH were 9.3 μg/dl (reference range; 5.7–11.1), 0.92 ng/ml (reference range; 0.76–1.50) and 4.82 μU/ml, respectively.

Patient 2

A 72-year-old male patient was referred to us for evaluation of a thyroid nodule. The patient had routinely gargled with povidone iodine three times a day for the last 4 years. Since the TSH level was slightly increased to 7.43 μU/ml, he was advised to stop gargling. Ultrasonographic examination of the thyroid revealed a slightly enlarged goiter with non-homogeneous density. When thyroid function was re-examined 3 weeks after cessation of gargling, the serum levels of TSH (1.79 μU/ml), free T3 (3.23 pg/ml), and free T4 (1.17 ng/dl) returned to the reference ranges.

Urinary excretion of iodine in patient 1 and 20 normal subjects

Since no data were available on urinary excretion of io-

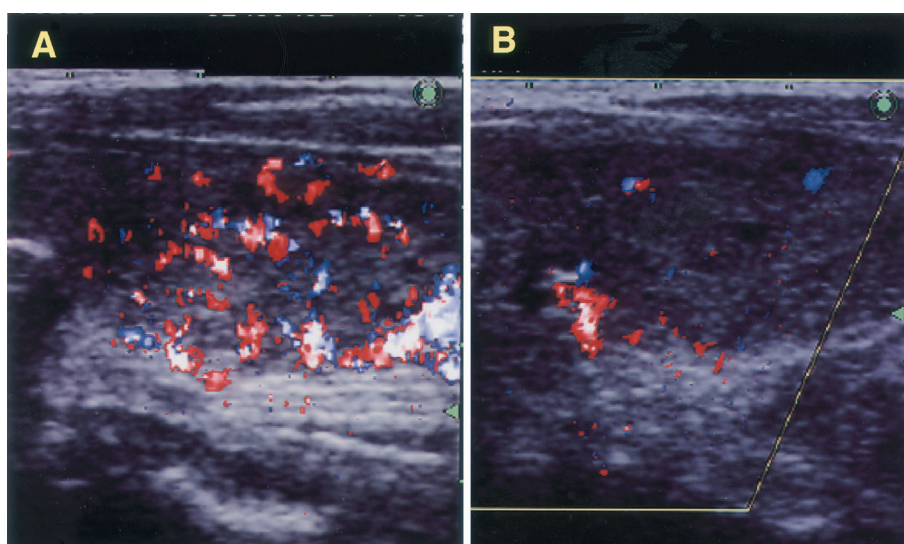


Figure 2. Color Doppler ultrasonography of the thyroid gland. Color Doppler flow ultrasonography revealed an increased blood flow of the thyroid gland in Patient 1 (the left lobe, longitudinal view) when his TSH was elevated (panel A), whereas it showed normal blood flow when he became euthyroid (panel B).

Table 1. Urinary Excretion of Iodine in 18 Normal Subjects

	Urinary iodine concentration (mg/L)	Urine volume (L/day)	creatinine (g/day)	Urinary excretion of iodide	
				(mg/gCr)	(mg/day)
Males (N=10)					
(-)	0.35±0.34	2.12±0.75	1.48±0.38	0.47±0.41	0.64±0.54
(+)	2.36±1.03*	2.04±0.81	1.63±0.53	3.17±2.00*	4.34±1.43*
Females (N=8)					
(-)	0.45±0.41	1.54±0.57	1.00±0.26	0.82±1.16	0.70±0.77
(+)	3.17±1.44*	1.62±0.56	1.01±0.29	5.35±3.84*	4.93±2.76*
Total (N=18)					
(-)	0.40±0.36	1.86±0.73	1.27±0.41	0.62±0.82	0.66±0.63
(+)	2.72±1.26*	1.85±0.72	1.36±0.53	4.14±3.07*	4.60±2.07*

(-) without gargling, (+) with gargling

* P<0.01, gargling (-) vs. (+)

dine in normal subjects gargling three times a day (5), these data were determined in 20 healthy subjects before and after gargling three times a day with povidone iodine. The volunteers were 10 healthy male subjects (25-64 years old) and 10 healthy female subjects (24-72 years old). This study was approved by the Ethics Committee of TWUM. All participants gave informed written consent. The subjects were asked to take a usual Japanese diet except for seaweed (particularly kombu), and urine samples were collected from 8 : 00 AM on Sunday to 8 : 00 AM on Monday. On another weekend, they were asked to gargle three times with 20 ml of a diluted gargle solution for 15 seconds after each meal, namely three times a day. The gargle solution was made with 4 ml of povidone-iodine diluted to 60 ml in tap water. After gargling, the mouth was not rinsed with water. Urine was collected in the same way and stored at -20°C. Iodine concentration was determined simultaneously according to the Ohashi method (7). Creatinine concentration was

determined in Special Reference Laboratory (Tokyo). Statistical significance was analyzed by Student's *t* test.

Among the 20 subjects who participated in the study, 2 subjects were excluded from analysis, because they apparently did not correctly follow the instructions. As shown in Table 1, urinary excretion of iodine in the 10 male and 8 female subjects was 0.64±0.54 mg and 0.70±0.77 mg (mean±SD) per day, respectively before gargling. It increased to 4.34±1.43 mg (range: 1.57-6.59 mg/day) and 4.93±2.76 mg per day (range: 2.69-10.1 mg/day), respectively, after gargling three times a day. When both data were combined, urinary excretion of iodine in 18 normal subjects were 0.66±0.63 mg/day before gargling and 4.60±2.07 mg/day, suggesting that about 5% of 82 mg iodine applied to the oral cavity (three times of 7 mg/ml×4 ml) was absorbed or swallowed, and excreted into urine by the next morning.

Patient 1 was unwilling to participate in this study, but admitted that he gargled routinely without diluting sufficiently with water as recommended in the guideline. Therefore, we estimate that the urinary excretion of iodine in the patient probably exceeded 5 mg/day.

Discussion

Povidone iodine (poly [(2-oxopyrrolidin-1-yl) ethylene] iodine) (Isodin Gargle), is a potent antiseptic with bactericidal, fungicidal, and viricidal properties, and has been widely used for gargling in Japan. It is recommended to gargle using 2 to 4 ml of the original solution diluted in 60 ml of water to prevent upper respiratory infections. It is also recommended to gargle several times a day. Since the original solution contains 7 mg/ml iodine, 3-5 gargling sessions using 14-28 mg iodine-containing mouthwash would consume 42-140 mg iodine per day. Although most of the

mouthwash would be spat out, a small proportion of iodine would be swallowed. Previous studies have reported that a mouthwash of povidone iodine used 4 times daily for a short period (2 weeks) or once daily for a prolonged period (24 weeks) did not affect thyroid function (1, 8).

Usually, when a large amount of iodine is given to normal subjects, acute inhibition of both thyroid hormone synthesis and release occurs (the Wolff-Chaikoff effect), as demonstrated *in vivo* and *in vitro* (9, 10). Prolonged administration of iodine is, however, usually associated with relief of this inhibition, a phenomenon termed "escape". In certain susceptible patients, however, the thyroid cannot escape from the transient inhibitory effect of iodine, and primary hypothyroidism may develop after prolonged iodine administration, as was observed in the present patient (1, 3). The pathogenesis of this escape phenomenon is at least partly due to the decreased expression of the sodium iodine symporter (NIS), as recently demonstrated in rats *in vivo* (11) and in human thyroid follicles *in vitro* (12). As reported by thyroidologists at Kyushu University (13), iodine-induced hypothyroidism resolves spontaneously and rapidly after withdrawal of iodine. Indeed, the serum level of TSH decreased rapidly by 50% or more in patients with iodine-induced hypothyroidism 6.1±3.1 days after the withdrawal of iodine (13). Therefore, it is highly likely that the serum level of TSH in the present patient would have been much higher than 93 µU/ml before his admission.

As is well known, povidone iodine-induced hypothyroidism also develops in a few patients who use it as a local disinfectant for perineal fistula, decubitus ulcer, the insertion site of a central vein catheter, or the urinary orifice, where iodine is easily absorbed (14, 15). This side effect is more prevalent in infants (16, 17), patients on peritoneal dialysis (18), and burn patients (19). However, it elicits no adverse effects in nurses with intact skin, even if they repeatedly disinfect their skin during their routine work (20).

In accordance with previous data reported from central Japan (21), urinary excretion of iodine in the present 18 normal subjects who took a usual Japanese-style diet was 0.56±0.46 mg/day. After gargling three times a day according to the instructions provided in the package leaflet, the urinary excretion of iodine was increased to about 5.0 mg/day. Ader et al (1) reported that urinary excretion of iodine increased from 0.161±21 to 2.744±0.409 mg/g creatinine, when individuals gargled twice with 10 ml of 5% povidone iodine solution for 15-30 seconds between 10 : 00 and 14 : 00. How-

ever, it is difficult to compare their data with ours, because in their study urine was collected only in the morning.

It is empirically known that inorganic iodine at a daily dose of 5-10 mg per day acutely elicits the Wolff-Chaikoff effect in patients with active Graves' disease (22). A prospective study has revealed that when 27 mg of iodine was taken for 28 days in 10 normal subjects, serum TSH levels increased significantly, with a small decline in the serum free T4 concentration (23). It is well known that the population living along the coast in Hokkaido, where goitre is endemic due to an excessive intake of kelp, excrete more than 20 mg iodine into the urine daily (24). In patients with life-threatening arrhythmia, who took amiodarone at a daily dose of 100-200 mg, about 6-8 mg/g creatinine of iodine was excreted into urine (25), and nearly 10% of the patients became hypothyroid. Compared with these data, the amount of iodine taken by the present patient 1 was not so excessive. Therefore, we speculate that the patient's thyroid gland was very susceptible to the inhibitory effects of iodine derived not only from povidone iodine but also from kombu. Although the anti-thyroid antibodies have been consistently negative in the present case, inhomogenous echoic lesion in the thyroid gland suggests that the patient may have focal lymphocytic thyroiditis (26, 27). As reported by Tajiri et al (28) and Kasagi et al (29), some patients with iodine-induced, reversible hypothyroidism have focal lymphocytic thyroiditis proved histologically by thyroid biopsy even though antibodies against microsomes, thyroglobulin, and/or peroxidase are negative.

In summary, as long as gargling with povidone iodine is performed according to the guidelines given in the drug package insert, the urinary excretion of iodine is about 5 mg at most, and the majority of normal subjects will remain euthyroid. However, in certain susceptible subjects, moderate to severe iodine-induced hypothyroidism may develop, particularly when gargling is done for a prolonged period, as in the present case. However, this hypothyroidism resolves spontaneously and rapidly upon discontinuation of the gargling.

We thank Dr. Toshinori Ohashi (Hitachi Chemical Co., Hitachi-shi, Japan) for advice about measuring the urinary concentrations of iodine. This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (17590967).

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