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±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

(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-
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).

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.

Patient 2

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Urinary excretion of iodine in patient 1 and 20 normal subjects

Since no data were available on urinary excretion of io-
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

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

(-) without gargling, (+) with gargling

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

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 was 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 iodide symporter (NIS), as recently demonstrated in rats in vivo 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 10.5 mg/day after gargling. 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.

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References


4. Drug package insert for povidone-iodine (Standard commodity classification number of Japan; #87226), Meiji Seika Kaisha, Ltd, Tokyo, Japan.


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