\textbf{125I Uptake Competing with Iodine Absorption by the Thyroid Gland following Povidone-Iodine Skin Application}

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\textbf{Abstract:} Povidone-iodine solution is widely used to disinfect the skin surface or prevent suppuration during human and animal surgery. Using radioisotope \textsuperscript{125I}, we examined whether iodine may be absorbed and then concentrated in the thyroid gland when povidone-iodine solution is applied to the skin of rats or mice. The competition for \textsuperscript{125I} uptake was examined in mice and rats after the application of povidone iodine to the skin. We also traced the process of absorbed \textsuperscript{125I} in the thyroid gland during the fixation for tissue preparations. Povidone-iodine applied to the skin significantly reduced the uptake of \textsuperscript{125I} both in mice and rats. Significant flux of \textsuperscript{125I} from the thyroid gland in povidone-iodine treated animals was noted during the thyroid fixation of tissue preparations. From these results, povidone-iodine application to the skin instead of stable KI administration may be practical for preventing the uptake of \textsuperscript{125I} by the thyroid gland during \textsuperscript{125I} compound administration for medical therapy. In animal experiments concerning thyroid functions, careful attention must be paid when povidone-iodine is used for disinfection in animal surgery.

\textbf{Key words:} disinfection, \textsuperscript{125I} uptake, povidone-iodine, skin, surgery, thyroid gland

\textbf{Introduction}

Povidone-iodine is a water soluble complex. It has sterilizing effects like those of free iodine. Povidone-iodine kills gram-positive and gram-negative bacteria, including antibiotic-resistant organisms, as well as fungi, viruses, protozoa and yeasts. Povidone-iodine exerts more prolonged germicidal action than ordinary iodine solution and its microbicidal action persists in the presence of blood, serum and pus.

Povidone-iodine is widely used in animal experiments and human surgery \cite{4} and particularly for the newborn as a broad spectrum topical germicide \cite{3, 11}. It is used for preparing the skin prior to minor surgical procedures, for covering open wounds and exposed membranes and enhancing eschar formation. The absorption of iodine and systemic toxicity have been reported as due to the use of povidone-iodine on burn wounds \cite{4, 7, 10}.

We found that the iodine from povidone-iodine may be absorbed during animal experiments when using povidone-iodine for disinfection during surgery. Using

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Table 1. 125I uptake by the thyroid gland after povidone-iodine application to rat skin

<table>
<thead>
<tr>
<th>Group</th>
<th>Thyroid</th>
<th>Blood/g</th>
<th>Thyroid/Blood</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>428704.0 ± 4347.1 (4)</td>
<td>11288.6 ± 137.7 (4)</td>
<td>37.97 ± 0.07 (4)</td>
</tr>
<tr>
<td>Povidone-iodine</td>
<td>201485.3 ± 28228.9 (4)**</td>
<td>11761.0 ± 539.0 (4)</td>
<td>17.53 ± 3.00 (4)**</td>
</tr>
</tbody>
</table>

Values are the means ± S.E.M. The number of rats is indicated in parentheses. Povidone-iodine was applied one time/one day on the skin with 10 mm2. 125I was intraperitoneally injected 2 hr after the povidone-iodine application. The blood was collected from the jugular vein under ether anesthesia and the thyroid gland was subsequently removed. 125I in the blood and thyroid was counted for 0.1 min in a gamma counter. Radioactivity and the ratio of thyroid/blood (p<0.01) in the control and povidone-iodine groups differed significantly (Student’s t-test).

radioisotope 125I, an examination was made to determine whether povidone-iodine is absorbed and concentrated by the thyroid gland when povidone-iodine solution is applied to the skin of rats or mice. We also traced the course of absorbed 125I in the thyroid gland during fixation for tissue preparations.

Materials and Methods

Animals: The animals used were male Wistar-Imamichi rats (The Imamichi Institute for Animal Reproduction; Ohmiya, Japan) and mature male BALB/c mice (inbred in our laboratory) 9–11 weeks of age. They were kept in an air-conditioned room (temperature: 24 ± 1°C, humidity: 50–60%) artificially illuminated daily from 06:00 to 20:00 hr. Rat chow (CMF, Oriental Yeast Co., Ltd., Tokyo, Japan) and water were available ad libitum.

Experimental procedure: Rats were used in the first experiment. The rats were administered 0.1 ml of povidone-iodine solution (Iodine solution, 1% of iodine solution; Meiji Seika Co., Ltd. Tokyo, Japan) once/day to denuded skin over a 20 mm2 area. This was followed by single injections of 110 KBq 125I-Iodine (IMS 30; Amersham, USA) 2 hr after the povidone-iodine application. Blood samples were collected from the jugular vein under ether anesthesia. The thyroid glands were subsequently removed after euthanasia by ether anesthesia. The thyroid glands were weighed and washed in physiological solution. 125I in the blood and thyroid gland was counted in a γ-ray counter.

Mice were used in the second experiment. The mice also were administered 0.1 ml of povidone-iodine solution once/day or twice/two days to denuded skin over a 15 mm2 area. In addition to the procedures in the rats described above, the following procedures were conducted. 125I in the thyroid gland was counted during the fixation. The thyroid glands were then fixed in 20% neutral buffered formalin for 3 days and embedded in paraffin wax. The fixed samples were embedded in paraffin, cut into 7 mm thick sections, deparaffinized and emulsified with an autoradiographic emulsion (ET2F; Fuji Film, Japan). After being completely dried, the sections were exposed to silver grains for 8 days at 4°C. This was followed by routine staining with hematoxylin.

Results

1. Uptake of 125I following povidone-iodine application to rats

The results of this treatment are shown in Table 1. No differences between the control and povidone-iodine application groups could be observed in the 125I counts in blood. 125I uptake counts in the thyroid gland in the two groups differed significantly. The povidone-iodine application group showed significantly decreased uptake. Uptake by the thyroid gland in the povidone-iodine application group was about 1/2 that in the control group. Thyroid/blood in the treated group was significantly less than that in the control group (treated; 17.53 vs. control; 37.97).

2. Uptake of 125I following povidone-iodine application to mice

The results are shown in Table 2. Significant differ-
ABSORPTION OF IODINE BY THE THYROID GLAND THROUGH THE SKIN

Table 2. Effects of povidone-iodine application to mouse skin on $^{125}$I uptake by the thyroid gland

<table>
<thead>
<tr>
<th>Group</th>
<th>Thyroid</th>
<th>Blood/g</th>
<th>Thyroid/Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>197292.3 ± 50022.0 (3)</td>
<td>48725.0 ± 9494.2 (3)</td>
<td>4.20 ± 1.44 (3)</td>
</tr>
<tr>
<td>2</td>
<td>15722.6 ± 2851.2 (3)**</td>
<td>71205.0 ± 15616.8 (3)</td>
<td>0.22 ± 0.02 (3)**</td>
</tr>
<tr>
<td>3</td>
<td>19421.3 ± 6166.7 (3)**</td>
<td>54713.3 ± 20508.4 (3)</td>
<td>0.40 ± 0.15 (3)**</td>
</tr>
</tbody>
</table>

Values are the means ± S.E.M. The number of mice is indicated in parentheses. Povidone-iodine was applied one time/one day (group 2) or two times/two days (one time/one day for two days; group 3) on the skin with 10 mm$^2$. Group 1 are the intact controls. $^{125}$I was intraperitoneally injected 2 hr after the povidone-iodine application. The blood was collected from the jugular vein under ether anesthesia and the thyroid gland was subsequently removed. $^{125}$I in the blood and thyroid was counted for 0.1 min in a γ-ray counter. Radioactivity and the ratio of thyroid/blood were significantly different (p<0.01) in group 1 from those in groups 2 and 3 (Student’s t-test).

3. $^{125}$I flow in the thyroid gland during fixation

The results are shown in Fig. 1. The effluent of $^{125}$I during a 6-day fixation significantly differed among the three groups. The control group showed little change in the effluent rate during the 6-day fixation. On the sixth day, the remaining $^{125}$I rate in the thyroid gland was 88.6%, but group 2 showed a marked reduction on the first day of 50.5%, and then a slower reduction from the first to sixth day. The greatest $^{125}$I flux from the thyroid gland was for group 3, showing remaining $^{125}$I count in the gland from the first day (50.5%) to third day (1.8%). In this group, no change was found from the third to sixth day.

4. Microscopic autoradiography of the thyroid gland

The results are shown in Fig. 2. Many silver grains were found in a section of the control group (Fig. 2A), but some silver graying was observed in a section obtained from group 2 (Fig. 2B), and a few silver grains were noted in a section obtained from group 3 (Fig. 2C). The silver grains had clearly developed more strongly in the section obtained from the control than in those obtained from groups 2 and 3.
Discussion

It is evident from the present results that 1) the skin absorbs iodine following povidone-iodine application, 2) absorbed iodine reaches the thyroid gland, 3) the iodine competes with the uptake of \( {^{125}}I \), either preventing or inhibiting this uptake, and 4) iodine causes \( {^{125}}I \), following its uptake, to flow again from the thyroid gland during formalin fixation.

The radioactivity of \( {^{125}}I \) in the thyroid gland in rats and mice differed. These results indicated a reverse correlation between the uptake of \( {^{125}}I \) by the thyroid gland and the amounts of applied povidone-iodine applied, because it is presumed that a greater amount of povidone-iodine was given to mice per body weight than in rats.

In the results shown in Fig. 1, a temporary uptake of \( {^{125}}I \) by the thyroid gland is noted, because much more elution of \( {^{125}}I \) from the glands during the fixative process was observed in the povidone-iodine treated mice (groups 2 and 3). The elution of \( {^{125}}I \) from the thyroid gland had a positive relationship with the amounts of povidone-iodine applied because much more \( {^{125}}I \) elution was noted in group 3 than in group 2. We speculate that elution of \( {^{125}}I \) from the gland may occur during the fixative process because of the disorder of iodine organization and incorporation into the thyroid hormones under the condition of excessive \( {^{125}}I \). This phenomenon possibly means that \( {^{125}}I \) was not fully incorporated into the cells of the thyroid gland in the povidone-iodine treated mice.

The findings of this study provide a possible basis for effective methods of povidone-iodine application to the skin [8]. The oral pre-administration of stable KI has been clinically carried out to reduce the uptake of \( {^{125}}I \) compounds into the thyroid gland for inspection or therapy both in man and animals. The clinical application of povidone-iodine solution may be carried out in preference to KI administration.

Povidone-iodine administration can be easily carried out in animal experiments. Continued absorption and some accumulation of iodine through the skin apparently occurs as a result of a long or frequent use of povidone-iodine. In view of the present data, povidone-iodine should be used with the utmost caution during surgical experiments on laboratory animals for studying thyroid function.

Iodine is a requisite substrate for thyroid hormone biosynthesis since both thyroxin and triiodothyronine are components of their molecules [5]. By applying povidone-iodine solution to the skin, the thyroid function may be disordered as a result of hormone synthesis inhibition due to the iodine. Pyati et al. [11] first reported a significantly increased serum iodine in two infants with wounds treated with povidone-iodine. No significant changes in the thyroid function could be detected [11]. Chabrolle and Rossier [3] reported five cases of hypothyroidism following topical application, and Castaing et al. [2] described twelve cases of iodine-induced hypothyroidism among thirty-six infants at various stages of gestation, treated with topical povidone-iodine. Dysfunction was most severe in immature infants. In the newborn, the skin layer is very thin and its permeability [9] facilitates mercury injection, but this has recently been shown to result in tragic hexachlorophene encephalography [6].

As already mentioned, povidone-iodine has harmful effects on the infant thyroid gland in humans. We therefore have to take great care in experiments analysing the function of the thyroid gland after using povidone-iodine. Particularly careful attention should be paid during surgery on pregnant and newborn animals when using povidone-iodine.

References


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Fig. 2. Microscopic autoradiography of the thyroid gland injected with \( {^{125}}I \) in the controls and povidone-iodine application mice (one time/one day and two times/two days). A, Control (intact) group; B, povidone-iodine application group with one time/one day; and C, povidone-iodine application group with two times/two days.