

## Thyroid Blockade during a Radiation Emergency in Iodine-rich Areas: Effect of a Stable-iodine Dosage

Noboru TAKAMURA<sup>1\*</sup>, Yoshihiro NAKAMURA<sup>4</sup>, Katsu ISHIGAKI<sup>4</sup>, Jitsuro ISHIGAKI<sup>4</sup>, Mariko MINE<sup>3</sup>, Kiyoshi AOYAGI<sup>1</sup> and Shunichi YAMASHITA<sup>2</sup>

### Thyroid gland/Radiation emergency/Iodine-rich areas/Potassium iodide.

We examined the effect of stable iodine on thyroid gland blockade in patients with hyperthyroidism in order to make a preliminary evaluation of the appropriate dose of iodine prophylaxis in the event of a radiation emergency in Japan in which radioiodine is released to the environment. Eight patients were orally given single doses of 50 mg or 100 mg of potassium iodide, which contained 38 mg and 76 mg of iodide, respectively. Both doses significantly suppressed a thyroid uptake of <sup>123</sup>I for 24 h ( $p = 0.03$ ). The protective effects at 24 h were 73.3% and 79.5%, respectively. No side effects were observed during the trial. The present study demonstrates that a single oral administration of 38 mg of iodide produces a thyroid-blocking effect equivalent to that of 76 mg of iodide, suggesting that a reevaluation of the stable iodine dosage during radiation emergencies in iodine-rich areas such as Japan is warranted.

### INTRODUCTION

It is well known that an increased incidence of thyroid cancer had been observed among A-bomb survivors in Hiroshima and Nagasaki.<sup>1)</sup> Furthermore, after the accident at the Chernobyl nuclear power plant, there has been a marked increase in pediatric thyroid cancer, presumably as a result of environmental dispersion and ingestion/inhalation of radioiodine, especially of <sup>131</sup>I.<sup>2,3)</sup> These findings strongly suggest a causal relationship among radiation, radioiodine, and the subsequent late onset of thyroid cancer.

There are 24 isotopes of iodine, <sup>117</sup>I to <sup>140</sup>I, and all except <sup>127</sup>I are radioactive. Among them, <sup>131</sup>I (half-life, 8.06 d) may play the most important role, since during a radiation emergency such as a breach-of-containment nuclear reactor accident it is released to the environment in large amounts and emits beta rays and gamma rays. If the accumulation of <sup>131</sup>I in the thyroid gland is to be minimized, it is necessary to achieve an effective thyroid blockage by stable iodine administration as soon as possible after the radiation incident. At the time of the Chernobyl accident, though potassium iodide (KI) was available in the former USSR, poor communication and gen-

eral reticence about the accident prevented the effective distribution of KI.<sup>4)</sup> The expeditious implementation of the procedures for thyroid blockade by stable iodide is clearly very important in emergencies of this kind.

In 1977, the International Atomic Energy Agency (IAEA) established an intervention criterion for a radiation emergency of an effective dose equivalent (EDE) of 100 mSv.<sup>5)</sup> In the United States, the Food and Drug Administration (FDA) and the National Council on Radiation Protection and Measurements suggested that 100 mg of iodide might be given daily, until a risk of significant exposure to radioiodines by either inhalation or ingestion no longer exists.<sup>6)</sup> Furthermore, after the nuclear reactor accident at the Three Mile Island facility in 1979, Sternthal *et al.* studied the effect of various doses of sodium iodide on thyroid radioiodine uptake and reported that a single administration of 30 mg of stable iodide could sufficiently suppress <sup>123</sup>I accumulation for 24 h<sup>7)</sup>.

In 1989 (and again through an update in 1999), the World Health Organization (WHO) reviewed the issue of KI usage and recommended that once intervention is decided on, stable iodide should be promptly given to all children, lactating mothers, and then adults less than 40 years old. These activities would be based on the emergency plans and the predetermined intervention level in each country. WHO outlines recommended KI doses as follows: a full 130 mg pill for individuals over 12 years old, 65 mg for children 3 to 12 years old, 32 mg for babies 1 month to 3 years old, and 16 mg for newborns up to 1 month old.<sup>6)</sup> In close agreement with these guidelines, the FDA recommends the following doses: a full 130 mg pill for adults, 65 mg for children 3 to 18 years old, 32

\*Corresponding author: Phone: +81-95-849-7066,

Fax: +81-95-849-7069,

E-mail: takamura@net.nagasaki-u.ac.jp

<sup>1</sup>Department of Public Health, <sup>2</sup>Department of Molecular Medicine and <sup>3</sup>Biostatistics Section, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan; <sup>4</sup>Ishigaki Thyroid Clinic, 217-1 Matsushiro-machi, Hamamatsu 430-024, Japan.

mg for babies 1 month to 3 years old, and 16 mg for newborns up to 1 month old.<sup>8)</sup>

It is worth noting, however, that the applicable standards of KI usage may differ from the suggested ones, depending on the natural iodine supply in various countries. For example, Japan is one of the iodine-richest areas in the world,<sup>9)</sup> and the stable iodine dosages for thyroid blockade may therefore warrant reevaluation. Previously, we have substantiated the necessity of thyroid blockade in the event of radiation emergency even in iodine-rich areas, since the blockade achieved strictly by an iodine-rich diet is generally inadequate.<sup>10)</sup> In this paper, we report the results of a preliminary study of the effect of a single administration of stable iodide on <sup>123</sup>I thyroid uptake during 24 h in order to evaluate the appropriate dose of KI in a radiation emergency.

## MATERIALS AND METHODS

### Study participants

Studies were carried out with eight patients who had hyperthyroidism (one male and seven females), age range 15–59 years old ( $39.0 \pm 13.6$ , mean  $\pm$  SE), at the Ishigaki Thyroid Clinic, Hamamatsu, Japan. Pregnant women were not included. The diagnosis in each patient was confirmed by the measurement of hormonal level and antibody titer (fT4 and TSRAb) and clinical examination. All but one patient have never been treated with antithyroid drugs, and one patient has had an experience of medication with methimazole, but had stopped it three months before the trial. The mean thyroid volume determined by ultrasound was  $32.8 \pm 12.8$  cm<sup>3</sup>.

Ethical approval was obtained from the appropriate committee of the Nagasaki University School of Medicine (project registration no. 14032639). An informed consent was obtained from each patient before the study. During trials, no complications such as hypersensitivity reactions were observed.

### Thyroid uptake of <sup>123</sup>I and administration of KI

We used <sup>123</sup>I rather than <sup>131</sup>I because of the far shorter half-life of <sup>123</sup>I (13.3 h) and therefore the lower exposure to the thyroid. A dose of 7.4 MBq of <sup>123</sup>I (Japan Radioisotope Association, Tokyo) was given orally for the baseline and blockade measurement of radioiodine thyroid uptake.

All data were acquired on a Toshiba GMS-7100 camera operating in the whole-body scanning mode (scan time 30 min, 15 cm from the thyroid). A high-energy parallel-hole collimator was employed. An aliquot of the administered activity, placed in a water-filled neck phantom 12.5 cm diameter, was imaged under exactly the same conditions as the patient. Following the acquisition of the images, the appropriate thyroid and background regions were drawn to allow a measurement of uptake.

The thyroid uptake was calculated as the percentage uptake of the administered dose and measured 3 h and 24 h after the

<sup>123</sup>I was orally administered. Then 3 d to a week later the second dose of 7.4 MBq of <sup>123</sup>I was given, followed one hour later by an oral administration of either 50 mg (4 patients) or 100 mg (4 patients) of KI, which contained 38 mg and 76 mg of iodide, respectively, and measurements of uptake were performed.

Since the baseline at the second trials contained the “residual uptake” of the first trial, we determined the uptake levels at 3 h and 24 h as (uptake at 3 and 24 h) – (baseline uptake), respectively. All subjects carried out their usual daily activities during the study.

The reduction in thyroid achieved by blockade was expressed as the “protective effect,” calculated as [(thyroid uptake *without* blocking – thyroid uptake *with* blocking)/(thyroid uptake *without* blocking)]  $\times$  100 (%).<sup>11)</sup>

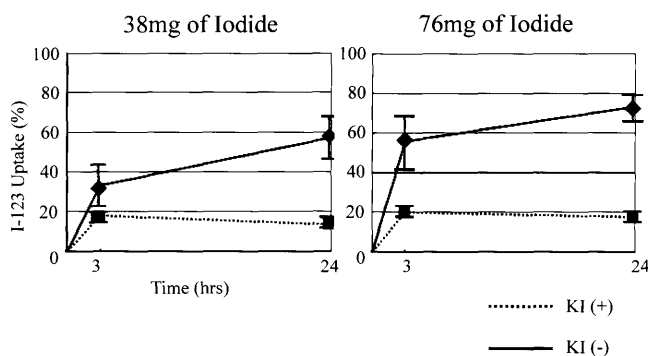
### Statistical analysis

Data were analyzed by use of the Statistical Analysis System, version 6.12 (SAS/STAT software package, SAS Institute Inc., USA). The mean uptake at 3 h and 24 h in the groups of subjects who received 50 mg or 100 mg of KI was analyzed by the Mann Whitney test. A *p* value of less than 0.05 was considered significant.

## RESULTS AND DISCUSSION

Mean baseline values for thyroid <sup>123</sup>I uptake were  $44.5 \pm 17.1\%$  at 3 h and  $65.3 \pm 11.2\%$  at 24 h. The uptake at these times, compared with control uptakes, was significantly reduced by the administration of a single dose of 76 mg of iodide ( $19.8 \pm 2.2\%$  and  $17.4 \pm 2.9\%$ , respectively, Fig. 1). The protective effect at 3 h and 24 h was 55.5% and 73.3%, respectively. Furthermore, the uptake was also significantly reduced by the administration of a single dose of 38 mg of iodide ( $18.0 \pm 3.5\%$  and  $13.4 \pm 2.8\%$ , respectively, Fig. 1). The protective effect at 3 h and 24 h accounted for 59.6% and 79.5%, respectively.

Previously, Sternthal *et al.* reported that the protective



**Fig. 1.** A 3 h and 24 h thyroid uptake of <sup>123</sup>I after a single administration of 76 mg (circles) and 38 mg (triangles) of stable iodide. The baseline values are indicated with (squares).

effect at 30 mg KI solution was more than 98% among euthyroid volunteers.<sup>7)</sup> The discrepancy between this study and ours might be caused by the selection of subjects, since we selected eight patients with active hyperthyroidism for study participants, whose uptakes are much higher than normal subjects.

For an effective iodine prophylaxis in a radiation emergency, the most important age group to target is young children. Children up to six years old should be strictly protected from the radiation fallout, according to experience from the accident at the Chernobyl nuclear power plant.<sup>12)</sup> Since thyroid blockade by stable iodide should have high priority as the first-line treatment in the event of a possible radiation emergency, the most appropriate KI dosage and regimen of administration should be reconsidered and possibly revised.

Noteboom *et al.* evaluated the <sup>123</sup>I thyroid uptake in chimpanzees aged 2 to 98 weeks.<sup>13)</sup> They concluded that a daily dose of 1.5 mg of stable iodide/kg of body weight and higher offers an optimal protection of the thyroid against exposure to radioactive iodine in infants. As previously pointed out, the physiological state of the thyroid of infant chimpanzees does not differ from that of human infants. According to the results, a sufficient dose for thyroid blockade in a child with 10 kg of body weight should be at least 15 mg of iodide. However, it is ethically impossible to confirm <sup>123</sup>I thyroid uptake in infants and children. Therefore we asked patients with hyperthyroidism, who needed the examination of <sup>123</sup>I thyroid uptake for their final diagnosis, to take part in this study. Of note, iodine kinetics is certainly different in patients with hyperthyroidism compared to euthyroid subjects.<sup>14)</sup>

Recently, Zanzonico and Becker created a computer model of iodine metabolism and systematically evaluated the time of administration of KI for an effective thyroid blockade.<sup>15)</sup> They demonstrated that the administration of KI 2 h and 8 h after <sup>131</sup>I yielded protective effects of 80% and 40%, respectively, with iodine-sufficient diets and 65% and 15% with iodine-deficient diets. They concluded that oral KI is effective only when administered within 8 h after the radioiodine intake. Although our current study was not performed on individuals with normal thyroid functions, our results showed that the prompt administration of stable iodide just after a radiation emergency can efficiently block the thyroid, even in patients with hyperthyroidism.

A special commission on iodine prophylaxis, now under the supervision of the Japanese government, is preparing a protocol for radiation emergency treatment in Japan. In this protocol, it is outlined that 76 mg of iodide should be given to individuals up to 40 years old. Our current results demonstrate that a single dose of 38 mg of iodide could suppress thyroid uptake of <sup>123</sup>I for 24 h as effectively as a 76 mg dose. Since we could not perform a similar trial in a group of subjects with normal thyroid function, it is difficult to unambiguously conclude that both doses can block the thyroid iodine uptake in a normal cohort. Larger doses seem to be more ben-

eficial in practice because the effect of iodine from the iodine stockpiles and of missed later administration are minimized. Furthermore, the timing relative to the radioiodine exposure of stable iodide administration should be reevaluated. For the establishment of cost-effective guidelines for iodine prophylaxis, therefore, further discussions and clinical trials are necessary.

Based on the Chernobyl experience,<sup>16)</sup> the most important points are that neonates and infants should be given a priority in iodine prophylaxis, and the problem of adverse reactions in them should not be ignored. Proper training and education of the population before a radiation emergency and prompt dissemination of appropriate instructions during such an emergency are also critical. The use of stable iodide as a means of protection from absorbing radioactive iodine released during a radiation emergency is dependent on other aspects of a sound disaster response plan, such as sheltering and evacuation based on expected exposure levels.

In conclusion, our preliminary results indicate the need for reconsidering the appropriate dose of stable iodide for thyroid blockade during a radiation emergency in iodine-rich areas such as Japan. Further investigation will be needed for the establishment of "evidence-based" guidelines for an iodine prophylaxis.

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