Urinary Iodide Excretion Measured with an Iodide-selective Ion Electrode: Studies on Normal Subjects of Varying Ages and Patients with Thyroid Diseases

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Abstract

As a part of studies concerning clinical application of the measurement of urinary iodide with an iodide-selective ion electrode, we report here the reference values for the iodide content or concentration in morning spot urine specimens from normal subjects of varying ages and studies with patients with thyroid diseases in Japan. The number distribution of the iodide content or concentration in the morning specimens appeared logarithmic normal in adults, children and infants. Normal ranges found in 95 per cent of populations of healthy subjects were 5.3 to 62.0 μ moles/g Creatinine (Cr) for adults, 5.3 to 42 μ moles/g Cr for children, and 1.9 to 56 μ M for infants, respectively. Urinary iodide concentrations in breast-fed infants varied widely compared with those in bottle-fed infants. Mean values were 16.4 μ M for breast-fed infants and 8.6 μ M for bottle-fed infants, and they were not statistically different. Urine samples from the infants with transient hypothyroidism, who had undergone amniocentesis showed extraordinarily high iodide concentrations, even though they were measured at 20th, 29th and 30th days after birth. Although urinary iodide excretion in patients with simple goiter was within normal limits, the mean was statistically lower than that in normal controls ($p < 0.001$). Because of the simplicity and rapidity of the electrode method, we strongly recommend it for use in examining iodide excretion in patients with various thyroid diseases.

Received October 13, 1987

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This study was financially supported by a Research Grant-in-Aid from the Ministry of Education, Science and Culture, Japan.

Although iodine deficiency is no longer a major world health problem, thyroid dysfunction associated with therapeutic and diagnostic iodine administration has been reported with increasing frequency (Blum *et al.*, 1974; Savoie *et al.*, 1975; Rodesch *et al.*, 1976; Theodoropoulos *et al.*, 1979;

Eason *et al.*, 1984; Leger *et al.*, 1984). In these cases, measurement of urinary iodide is necessary for diagnosis and treatment, because urinary excretion of iodide is the most valid index of iodine intake.

The classic chemical procedures for measurement of iodine are tedious, time-consuming and sometimes inaccurate at low levels of iodine, and collecting urine for a 24 hour period is obviously inconvenient for patients. Recently, we developed a simple and rapid method to measure iodide in urine with an iodide-selective ion electrode, and showed the usefulness of this electrode method as a laboratory procedure. We have also reported a good correlation between iodide concentrations in morning spot urine specimens and those collected over a 24 hour period (Yabu *et al.*, 1986). In this manuscript, studies on iodide concentrations in urine measured with the electrode method on normal subjects of varying ages and patients with thyroid diseases are described. Clinical application to the measurement of urinary iodide is also discussed.

Materials and Methods

Subjects and Specimens

Urine specimens from 127 normal adults (39 men and 88 women, aged from 18 to 57), 43 normal children (27 boys and 16 girls, aged 3 to 10) and 30 infants (18 males and 12 females) were studied. All of them were healthy and none had goiter on careful palpation by either internists or pediatricians. Of 30 infants, 23 were fed with breast milk and 7 were with market milk, respectively. Urine samples from 3 neonates after amniocentesis, and 24 patients with simple goiter (all women, aged from 11 to 32) were also examined. These 3 neonates were the patients recalled from the screening program for congenital hypothyroidism, and showed at least one of the clinical features of hypothyroidism, skin mottling, enlarged tongue or hypotonia. The diagnosis of simple goiter was made on finding a small, soft and diffuse goiter associated

with euthyroidism, that was assessed from serum concentrations of thyroxine (T_4), triiodothyronine (T_3) and thyrotrophin (TSH), and T_3 uptake test (T_3U). None of them showed positive thyroidal autoantibodies (anti-thyroglobulin and anti-microsomal antibodies). Urinary iodide excretion in a patient with goitrous hypothyroidism without anti-thyroidal autoantibodies was also examined. She was a 55-year-old female who had been treated with 60 mg of oxapium iodide (Esperan®), an anti-cholinergic drug, for approximately 2 years.

Morning spot urine from the first urination before breakfast was examined in adults and children, and spot urine in the morning in infants and neonates. Three neonates who had undergone amniocentesis were examined on the 20th, 29th and 30th days after birth, respectively. Urine samples from adults and children were usually taken on a habitual diet. In order to see serial changes in urinary iodide excretion on an unrestricted and a low iodine diet, urine specimens were taken from 9 normal adults every morning over a period of 2 weeks. Two to three specimens were taken from each individual patient with simple goiter over a one week period on an unrestricted habitual diet. All samples were stored at -20°C with tight stoppers until used.

Methods

Urinary iodide concentrations were measured with an iodide-selective ion electrode (Iodide-Selectrode®, Radiometer, Copenhagen, Denmark) and concentrations of urinary creatinine (Cr) were measured by the Jaffe's rate method with an autoanalyzer as described previously (Yabu *et al.*, 1986). Urinary iodide content was expressed as moles of iodide per gram of Cr times 1.0 (females) or 1.7 (males) in adults, according to the formula reported by Vought *et al.* (1963). In pre-adolescent children, iodine intake was assessed by moles of iodide per gram of Cr in both boys and girls (Clark *et al.*, 1951) and by only iodide concentrations in infants, since Cr excretion in infants is much lower than that in later life (Applegarth *et al.*, 1968) and renal function is not sufficient until the age of 1-2 years (Rubin *et al.*, 1949). Serum concentrations of thyroid hormones and TSH were measured with conventional radioimmunoassay kits, and anti-thyroidal autoantibodies were with Seroida-AMC and ATD kits (Fujirebio Inc, Tokyo), respec-

tively. Statistical analyses were performed by the Mann-Whitney U test.

Results

Iodide content in morning spot urine

Fig. 1 shows the number distribution of iodide content in morning spot urine

specimens from normal adults and children. Both appeared typical logarithmic normal distributions. Normal ranges found in 95 per cent of populations of healthy subjects were 5.3 to 62.0 with a mean of 23.8 μ moles/g Cr in adults and 5.3 to 42.0 with a mean of 21.7 μ moles/g Cr in children, respectively. There was no statistical difference in the urinary iodide content

Fig. 1. Iodide content in morning spot urine specimens from healthy adults and children. All of them were taken on a habitual unrestricted diet.

Fig. 2. Daily iodide excretion on an unrestricted and a low iodine diet. Samples were taken from 9 normal healthy adults every morning for a week on an unrestricted diet and for the next week on a low iodine diet.

in adults and children.

Daily change in iodide excretion on unrestricted and low iodine diet

As shown in Fig. 2, iodide content in urine samples from 9 normal volunteers on an unrestricted diet fluctuated according to iodine intake in food. On a low iodine diet, the iodide content in urine decreased by the 3rd day and persisted at a low level without fluctuation. The mean ($\pm$ SD) iodide content in morning specimens on an unrestricted diet was 37.6 ± 33.4 μ moles/g Cr (number of samples=63) from 9 normal volunteers over a week, and it decreased to 11.3 ± 5.3 μ moles/g Cr (number of samples=9), after iodine depletion for 6 days.

Iodide excretion in infants

The number distribution of the iodide concentration in urine specimens from 30 infants also appeared logarithmic normal (data not shown). The normal range found in 95 per cent of the population was 1.9 to 56 μ M with a mean of 14.6 μ M. As shown in Fig. 3, the urinary iodide concentration in infants fed with breast milk varied between 4.1 and 41.1 μ M with a mean of 16.4 μ M, and in infants

Fig. 3. The number distribution of iodide concentration in breast-fed and bottle-fed infants. The mean values in the two groups were not statistically different.

Table 1. Thyroid function tests and urinary iodide concentrations in 3 neonates with transient hypothyroidism

	age/sex	T ₄ (μ g/dl)	T ₃ U (%)	T ₃ (ng/dl)	TSH (μ U/ml)	Thyroidal autoantibodies	iodide concen- trations (μ M)
Case 1	16 days/F	1.4	25.5	94	>160	TG (-) MC (-)	675.4
Case 2	24 days/M	2.1	28.5	186	91.3	TG (-) MC (-)	57.2
Case 3	15 days/F	2.5	n.d.	96	264.3	TG (-) MC (-)	174.3

TG denotes anti-thyroglobulin antibodies, MC anti-microsomal antibodies. The urinary iodide concentration was examined on the 30th day for case 1, the 20th day for case 2 and the 29th day for case 3, respectively. n. d., not determined.

Normal ranges for infants (around a month old) in our laboratory are following: T₄: 7.2–14.8 μ g/dl, T₃: 163–283 ng/dl and TSH: 2.9–12.1 μ U/ml, respectively. T₃U value for infants was not obtained. Refere the normal range for adults (25.7–33.5%).

Fig. 4. Iodide content in morning spot urine specimens from normal controls and patients with simple goiter. Mean ages were 19.0 ± 1.4 years for normal controls and 18.4 ± 6.4 years for the patients, respectively.

fed with market milk there was a very narrow distribution between 4.7 and 12.1 μM with a mean of 8.6 μM . However, the mean values in the two groups were not statistically different. Three urine samples from the infants who had undergone amniotography showed an extraordinarily high iodide concentration, 57.2, 174.3 and 675 μM , respectively. Their thyroid function tests at the time of re-call are summarized in Table 1. After the diagnosis of hypothyroidism, they were treated with levothyroxine. The replacement therapy was discontinued after certain periods, because their thyroid function tests returned to normal.

Iodide excretion in patients with simple goiter

Fifty-five urine specimens from 24 young female patients with simple goiter were compared with those from age and sex matched controls who were 73 normal healthy young females, aged 18 to 27. As shown in Fig. 4, the iodide content in morning specimens from patients with simple

goiter (mean: 13.4 $\mu\text{moles/g Cr}$) was statistically lower than in normal controls (mean: 22.4 $\mu\text{moles/g Cr}$) ($p < 0.001$).

Iodide excretion in a patient treated with oxapium iodide

Three urine specimens obtained from a patient with goitrous hypothyroidism contained almost identical amounts of iodide i. e. 159.9, 154.0 and 151.4 $\mu\text{moles/g Cr}$, which were about seven times the mean value for normal controls. She had a prominent goiter, 6.5 cm in transverse width and increased TSH (16.4 $\mu\text{U/ml}$, normal range: 0.3–6.5 $\mu\text{U/ml}$). After discontinuation of the drug for 6 months, the goiter has disappeared in association with normal TSH. The urinary iodide excretion on her habitual diet ranged from 17.7 to 29.1 $\mu\text{moles/g Cr}$.

Discussion

As a part of a series of studies on clinical application of the measurement of

iodide in urine, we here describe the reference values for iodide content in morning spot urine specimens from normal subjects at various ages and studies of patients with thyroid diseases in Japan. The number distribution of urinary iodide content or concentration in specimens from normal adults, children and infants appeared logarithmic normal and there was no statistical difference between adults and children. On unrestricted habitual diet, urinary iodide content fluctuated according to iodine intake, as shown in Fig. 2. Therefore, frequent sampling should be done to estimate the iodide intake in each individual.

Since 1940 when Parmelee *et al.*, (1940) reported 3 cases of newborn infants with goiter, it has been said that maternal intake of excess iodine is one of the causes of congenital goiter and hypothyroidism (Hassan *et al.*, 1968; Carswell *et al.*, 1970). Therefore, we had been concerned that breast-fed infants in Japan might be exposed to much higher levels of iodine than bottle-fed infants, since a large amount of seaweed is often ingested by mothers on their habitual diet, and iodide from food is actively transported into breast milk (Vorherr, 1974; Colett *et al.*, 1984). However, studies in infants revealed that the urinary iodide concentration was not significantly different in breast-fed and bottle-fed groups, although samples from breast-fed infants varied over a wide range. It is noteworthy that the urinary iodide concentration of 3 infants after amniocentesis was extraordinarily high, even though it was measured on the 20th, 29th and 30th days after birth. Recently, 2 cases of transient neonatal hypothyroidism caused by maternal ingestion of excess seaweed have been reported (Tohoya *et al.*, 1987; Sakaguchi *et al.*, 1987). Because iodide-induced transient hypothyroidism requires neither extensive examinations nor life-long thyroid hormone therapy, we believe that it is worth measuring the urinary iodide con-

centration in neonates and their mothers, who showed increased TSH on the screening program.

It has been accepted worldwide that iodine deficiency is a major factor contributing to endemic goiter. Iodine excess has also been a cause of endemic goiter in Hokkaido (Suzuki *et al.*, 1965). And both iodine deficiency and excess have been reported to contribute to sporadic, non-toxic goiter (Agerback *et al.*, 1974; Trowbridge 1975). It is therefore interesting to examine the urinary iodide excretion in patients with simple goiter in Japan, where a large amount of iodine is taken in the habitual diet. Unexpectedly, the urinary iodide excretion in patients with simple goiter was within the normal range, but rather lower than that in normal controls ($p < 0.001$). Obviously this result does not mean that relative deficiency of iodine contributes to simple goiter in Japan, since the administration of iodine for 3 to 6 months did not cause the disappearance of goiter in those patients although it was done in only a few cases. It is possible to say, however, that excess iodine does not mainly contribute to sporadic simple goiter in Japan. Other factors including growth stimulators of immune origin might play an essential role in the development of goiter in these patients (Drexhage *et al.*, 1980; Valente *et al.*, 1983).

More than 50 kinds of drugs containing iodide are now widely used for diagnosis or therapy in Japan. Most of them are iodinated contrast media, which have been reported to cause goiter or thyroid dysfunction (Blum *et al.*, 1974; Rodesch *et al.*, 1976). Oxapium iodide contains 2.7 mg of iodide per 10 mg, and 16.2 mg of iodide had been administered to the patient for approximately 2 years. Mild hypothyroidism and goiter were obviously produced by this medicine, since her goiter has disappeared after discontinuation of the medicine, and TSH returned to normal. This type of

goitrous hypothyroidism might be very difficult to diagnose, since oxapium iodide itself is not a common drug which produces goiter and hypothyroidism, and the patient did not have an episode of excess iodine ingestion from food.

It is generally accepted that thyroid diseases in Japan have certain characteristic clinical features (Nagataki, 1970), although relationship between these features and excess iodine intake has not yet been revealed. And recently Yoshinari *et al.*, (1983) and Tajiri *et al.* (1986) reported that more than half of patients with primary hypothyroidism who had goiter and normal thyroidal radioactive iodine uptake became euthyroid spontaneously after dietary iodine restriction. Thyroid dysfunction associated with iodine intake seems to be more common than had been expected. We therefore strongly recommend the measurement of the iodide content in morning spot urine as a routine examination by the simple electrode method.

Acknowledgements

We thank Drs. Y. Fukuda, K. Miki, N. Amino, K. Ichihara, C. Hayashi and K. Kohoda for valuable advice; Ms. S. Yamada and Ms. N. Yokota for secretarial assistance; and Ms. F. Oka, Ms. K. Tsujimura and Ms. T. Hiya for generous help as volunteers.

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