Original Article

Effectiveness of a Spot Urine Method in Evaluating Daily Salt Intake in Hypertensive Patients Taking Oral Antihypertensive Drugs

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Kawasaki *et al*. developed a spot urine method (SUM) for evaluating daily salt intake using one pre-breakfast sample obtained after initial voiding upon arising. Their subjects were healthy persons who were not taking any regular medications. To determine whether SUM can be successfully used for patients taking antihypertensive drugs, we estimated daily salt intake in 73 hypertensive patients by SUM and by a food consumption method (FCM) when they were at home, and also by SUM in the hospital with a defined intake of 7 g of sodium chloride (NaCl). Forty-one patients took oral antihypertensive medications once daily, while 32 patients took none. Mean daily salt intakes by SUM during admission were 7–8 g of NaCl in both groups (95% confidence intervals: 5.0–10.6 g in the medication group; 5.2–11.1 g in the no-medication group), which corresponded well to the diet. In contrast, ambulatory daily salt intake by SUM varied widely (95% confidence intervals: 5.5–20.7 g in the medication group; 7.6–22.8 g in the no-medication group). However, the daily salt intakes determined by SUM and FCM correlated significantly with each other in the medication group (r=0.69, p<0.01) and the no-medication group (r=0.66, p<0.01). SUM is therefore a reliable method for evaluating daily salt intake in patients taking antihypertensive medication as well as unmedicated patients. (*Hypertens Res* 2006; 29: 397–402)

***Key Words*: antihypertensive drugs, salt intake, spot urine method, hypertension, food consumption method**

Introduction

A chronically high salt intake plays an important role in onset and maintenance of hypertension, while restriction of salt intake lowers blood pressure in hypertensive patients. Salt intake and restriction in hypertension have been subjects of recent reviews (*1–3*). Restriction of salt intake is a particularly important therapeutic lifestyle modification; authorities in various countries (*4*, *5*) including Japan (*6*) recommend a daily intake of less than 6 g of sodium chloride (NaCl). Daily salt intake has been estimated from food consumption data obtained by interview or diary methods, or from 24-h urinary sodium excretion. By either method, reliable results are fairly difficult to obtain. And unfortunately, most hypertensive patients do not undergo evaluation of salt intake by any method. Kawasaki *et al*. (*7*) developed a "spot" urine method (SUM) for evaluating daily salt intake using a urine specimen collected after the first voiding upon awakening, but before breakfast. Values obtained by the SUM correlated highly with those from determinations of 24-h urinary sodium excretion (r=0.73). The usefulness of the SUM has been confirmed in population studies (*8–11*) and in hypertensive patients who were taking no medicine (*12*, *13*). While calcium channel blockers (*14*), angiotensin-converting enzyme inhibitors, and diuretics (*15*) have a natriuretic action, α-blockers (*16*) have an anti-natriuretic action, and these differing effects presumably could affect daily salt intake estimated by SUM in med-

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Received November 15, 2005; Accepted in revised form February 21, 2006.

Table 1. Baseline Characteristics of Hypertensive Patients with and without Antihypertensive Medication

	Medication (n=41)	No-medication (n=32)
Male/female (number)	21/20	15/17
Age (years)	54±9	59±7
Height (cm)	161±8	159±9
Body mass index (kg/m^2)	26.1±3.4	25.1±3.2
Systolic BP (mmHg)	148±10	149±9
Diastolic BP (mmHg)	89±8	91±4
Total cholesterol (mg/dl)	204±41	204±33
HDL cholesterol (mg/dl)	49±14	57±26
Triglycerides (mg/dl)	158±97	122±50
Hemoglobin A_{1c} (%)	5.8±0.9	5.8±0.8
Serum creatinine (mg/dl)	0.82±0.22	0.70±0.14*
Urinary albumin excretion (mg/g Cr)	75±189	13±16*
Left ventricular mass index (g/m^2)	132±43	120±29

BP, blood pressure; HDL, high density lipoprotein; Cr, creatinine. *p<0.01 compared with medication group.

icated patients by altering the circadian rhythm of sodium secretion (*17*). Therefore, we here investigated whether or not the SUM is applicable to patients taking oral antihypertensive medications on a regular basis by comparing results with those in hypertensive patients who took no medicine.

Methods

Study Subjects

We recruited patients with one or more of three cardiovascular risk factors—hypertension, dislipidemia, and/or diabetes—who wanted to initiate lifestyle modifications involving diet and exercise in a 14-day inpatient hospital program. They were informed about the program through a pamphlet available in general practitioners' offices and health check centers in Iwate Prefecture, or *via* the Internet through the home page of our hospital. From among patients with essential hypertension seeking admission for this program from 2001 to 2004, we chose 73 subjects who satisfied three criteria. First, they were assessed at our clinic during a 3-month period before admission, undergoing SUM- and food consumption method (FCM)–based estimation of daily salt intake. Second, salt intake was limited to 7 g of NaCl daily during admission, with estimation of daily salt intake by SUM during the second week of admission. Third, during the observation period, patients did not take any medicine on a regular basis, with the exception of antihypertensive drugs in those already taking antihypertensive drugs, and the prescriptions of antihypertensive drugs were kept unchanged during the observation period. All subjects were given detailed information about the protocol, and provided their informed consent before enrollment.

Table 2. Daily Salt Intake by a Spot Urine Method (SUM) and a Food-Consumption Method (FCM) in Ambulatory and Inpatient Settings, by Medication Status

Salt intake	Medication (n=41)	No-medication (n=32)
Ambulatory		
SUM	13.1±3.8	15.2±3.8
FCM	11.9±2.6*	12.6±3.3**
Hospitalized		
SUM	7.7±1.3**	8.1±1.4**

Intake is expressed as g of NaCl per day. *p<0.05, **p<0.01 compared with the spot urine method under ambulatory conditions.

Procedures

A nutritionist described FCM to the subjects, and then, over 2 consecutive days, subjects took their usual meals and recorded the food they consumed in a diary. On the day following diary completion, they underwent determination of salt intake by SUM. They reported to our clinic at 8:30 AM for urine and blood sampling, after the first voiding upon awakening but before breakfast. The FCM diary was started between Monday and Wednesday to ensure that the spot urine would be collected on a weekday. The completeness of the submitted FCM diaries was checked by interviews with the nutritionist. During the hospital admission, patients again underwent examination of salt intake by SUM, arising at 6:00 AM and discarding urine from the first voiding. A urine sample was collected later, before breakfast at 8:00 AM. During admission, patients were advised to eat all foods provided but no others. Drinking water and weak Japanese tea were available ad libitum.

Measurements and Calculations

Using the spot urine specimen, we calculated daily excretion of sodium by the Kawasaki formula (*7*), which is based on the subject's gender, age, body weight, height, and sodium and creatinine concentrations in the urine sample. Because approximately 90% of sodium intake is excreted as urinary sodium (*18*), the daily excretion of sodium was considered equal to the daily sodium intake, which was expressed as g of NaCl per day as suggested by the Japanese Society of Hypertension Guidelines (*6*). With some modifications, the FCM was based on a method used in the Japanese National Nutrition Survey (*19*). Patients were asked to provide detailed descriptions of each food consumed, including the method of preparation and recipes whenever possible. Nutritionists checked submitted FCM records by interview, using various aids including models of foods, pictures, various types and sizes of spoons, cups, bowls, plates, and commercially sold cans and packets to assist the patient in specifying and quan-

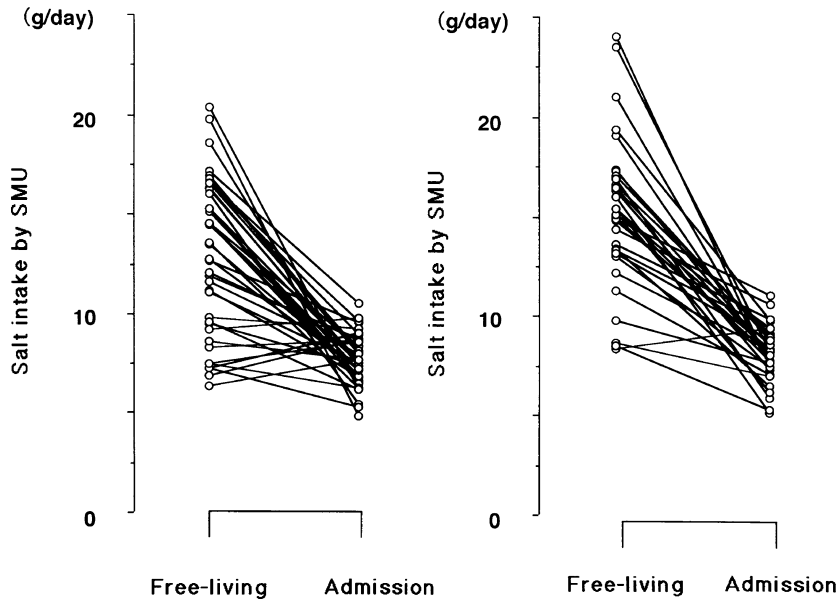

Fig. 1. *Individual patient data for daily salt intake estimated by a spot urine method (SUM) under ambulatory and inpatient conditions in the medication group (left) and the no-medication group (right). Salt intake is expressed as g of NaCl per day.*

tifying foods. Special attention was given to estimation of intake of soy sauce, table salt, miso, and pickles, since approximately 70% of the total amount of salt ingested by residents of Iwate Prefecture has been found to come from these items (*20*). Foods then were coded for computer analysis using the Food Composition Database (ICS, Morioka, Japan) based upon the Japan Food Composition Table (*21*). Urinary albumin concentration was measured by SRL laboratories (Tokyo, Japan) in a portion of the spot urine specimen. Blood pressure was taken as the mean of readings at the last three clinic appointments. The left ventricular mass index was determined according to the method of Devereux *et al*. (*22*).

Statistical Methods

Values are expressed as the means±SD. Gender distribution differences between the medication group and no-medication group were analyzed by the χ^2 test; the Mann-Whitney *U* test was used to compare other variables between these groups. The ambulatory and inpatient phases of the study were analyzed by Wilcoxon's test. The correlation between the daily salt intakes determined by the SUM and by the FCM under ambulatory conditions was assessed by univariate analysis. A *p* value less than 0.05 was accepted as indicating statistical significance.

Results

Subjects consisted of 41 patients taking oral antihypertensive drugs (medication group) and 32 patients not taking such drugs (no-medication group). Baseline characteristics of the two groups of subjects are presented in Table 1. No parameters were significantly different between the two groups except for serum creatinine concentration and urinary albumin excretion. In the medication group, 25 subjects (61%) took one antihypertensive drug; 13 (32%) took two in combination; 1 (2%) subject took three; and 2 (5%) subjects took four. Twenty-nine subjects took a calcium channel blocker (amlodipine, manidipine, cilnidipine, benidipine, or nifedipine); 13 took a diuretic (indapamide or trichlormethiazide); 11 took an angiotensin II receptor blocker (candesartan or valsartan); 4 took a β-blocker (betaxolol or atenolol); 4 took an angiotensin-converting enzyme inhibitor (perindopril or lisinopril); and 1 took an α-blocker (doxazosin).

The daily salt intake values determined by SUM and FCM are presented in Table 2. The medication and no-medication groups did not significantly differ in daily salt intake either, by the two ambulatory estimations or by the inpatient SUM. Daily salt intake by SUM in both groups was significantly lower during admission than in the ambulatory phase. The mean values of daily salt intake estimated by SUM during admission were 7–8 g of NaCl in both groups, and these values corresponded with the daily salt content of the diet.

The daily salt intake estimated by SUM was plotted individually for the ambulatory and hospitalized phases for patients in both groups (Fig. 1). Daily salt intake varied widely under ambulatory conditions (95% confidence intervals: 5.5–20.7 g of NaCl in the medication group; 7.6–22.8 g of NaCl in the no-medication group). Much less variability was seen during admission (95% confidence intervals: 5.0–10.6 g in the medication group; 5.2–11.1 g in the no-medication group).

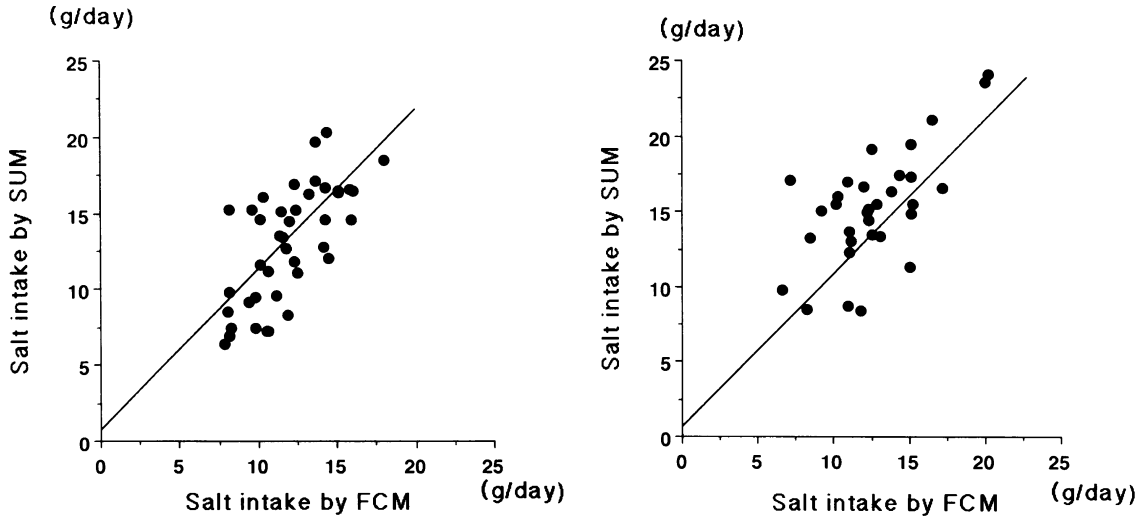

Fig. 2. *Relationship of daily salt intake estimated by a food consumption method (FCM) and by a spot urine method (SUM) in the medication group (left) and the no-medication group (right). Salt intake is expressed as g of NaCl per day. By univariate analysis, daily salt intake estimated by SUM was significantly correlated with intake by FCM in both the medication group (*$r = 0.69$, $p < 0.01$*) and the no-medication group (*$r = 0.66$, $p < 0.01$*).*

The ambulatory daily salt intakes by SUM and FCM were significantly correlated in both the medication group ($r=0.69$, $p<0.01$) and the no-medication group ($r=0.66$, $p<0.01$) (Fig. 2).

Discussion

We examined whether SUM yielded valid estimates of daily salt intake in patients taking antihypertensive drugs. Our observations indicated that the SUM results in such patients were valid. The daily salt intake estimated by SUM during admission was 7–8 g of NaCl in both groups, corresponding to the daily salt content in the diet. This was true even though the daily salt intake determined by the same SUM varied widely under ambulatory conditions. Under ambulatory conditions, the SUM and FCM results were correlated in both groups, and the mean daily salt intake determined by the SUM was similar to that obtained by FCM. Furthermore, these values were also similar to our previous data (12.5 g of NaCl) obtained by measuring 24-h urinary sodium excretion in residents of Iwate Prefecture with essential hypertension (*23*). This suggested that the present patients had a daily salt intake similar to that of previously studied hypertensive patients living in this same area.

Ambulatory individual daily salt intake varies considerably over time; Kawasaki *et al*. (*24*) reported that individual subjects' standard deviation for salt intake was 25–27% in estimates based on 24-h urine collections over 3 consecutive weeks. Accordingly, repeated measurements of daily salt intake are necessary to accurately evaluate daily salt consumption. SUM is noninvasive and is much easier for patients than 24-h urine collections or 24-h food-intake diaries (*25*). In ordinary practice, hypertensive patients taking medication periodically undergo urinalysis and blood sampling before breakfast; we would suggest that patients undergo evaluation of salt intake by SUM at the same time.

As for the reliability of SUM in evaluating daily salt intake, our inpatients consumed 7 g of NaCl daily. In a previous study, however, when dietary salt was estimated by the food consumed for 1 week in March 2004 using Standard Tables of Food Composition, it varied from 6.1 to 7.4 g of NaCl (S. Yamakuwa, personal communication). We evaluated inpatient salt intake by SUM after continuously controlled salt intake for 1 week, since the equilibration of sodium balance between intake and urinary excretion requires approximately 1 week (*26*). At that time, the 95% confidence interval of daily salt intake was approximately 5–10 g of NaCl in both groups, suggesting over- or underestimation by approximately 2–3 g of NaCl. One should keep in mind that this is also the case with 24-h urine collection, which is considered the most reliable method (*27*, *28*). Previous studies (*29*, *30*) have reported wide fluctuations in 24-h urinary sodium excretion in subjects whose salt intake is kept constant. Most often, variation is minimized by estimating daily salt intake from the mean of 24-h urinary sodium excretion determinations over 2–3 consecutive days to diminish day-to-day variations (*31*). This strategy was validated by Kawasaki *et al*. (*7*), who reported that the correlation coefficient between SUM and 24-h collection increased by 0.53 for a single day to 0.82 for a mean intake reflecting 3 consecutive days. Accordingly, SUM should be used with an awareness of its limitations. No current method for daily salt intake is superior to others in all

respects.

The present study suggested that SUM is applicable to patients taking oral antihypertensive medications once daily in the morning. Recently, because morning blood pressure surge was linked to adverse cardiovascular events (*32*), several investigators (*33*, *34*) proposed that these drugs be administered at bedtime rather than in the morning in order to reduce the early-morning surge. It remains to be seen whether SUM is accurate with such a medication schedule, or whether it is appropriate for patients with severe target organ damage including the kidney and patients in the accelerated phase of hypertension.

Some limitations of our study are apparent. We used the FCM for only two consecutive days to obtain control values to assess SUM results, since 2-day FCM has been routinely used in our hospital to estimate patient salt intake. To enhance reliability in future studies, a longer period of FCM might be used to derive the control values, such as the 4 days used in the INTERMAP study (*35*). Also, since our medication group consisted of patients who were taking no regular medications except for the antihypertensive drugs, the effects of other drugs on the validity of the SUM remain to be determined. Because the subject numbers were relatively small in the present study, we also could not estimate the effects of individual classes of antihypertensive drugs on the validity of the SUM. Further studies with larger numbers of patients may be needed to clarify these issues.

At present, SUM would appear to be effective for evaluating daily salt intake in patients taking oral antihypertensive medications once daily in the morning, as well as in unmedicated hypertensive and normotensive subjects.

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