Low Salt Intake and Changes in Serum Sodium Levels in the Combination Therapy of Low-Dose Hydrochlorothiazide and Angiotensin II Receptor Blocker

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Background: The present study was conducted to examine the association of dietary salt intake with changes in serum sodium (srNa) levels when angiotensin II receptor blocker (ARB) treatment is changed to the combination of ARB plus low-dose diuretic (hydrochlorothiazide [HCTZ]).

Methods and Results: In 88 patients (age 70±12 years), ARB treatment was switched to the combination therapy (same dosage ARB+12.5 mg/day HCTZ). The srNa level was measured before and 6 months after administration of the combination. The daily salt intake was estimated by the Kawasaki formula using second morning urine sample. The study subjects were divided into quintile ranges according to daily salt intake. The reduction in srNa levels by switching to the combination treatment was significant in subjects in the lowest quintile Q5 (≤8.9 g/day salt intake), but not in those in Q1–4 (28.1–9.3 g/day salt intake). Increases in serum creatinine and uric acid levels were significantly larger in the former group than in the latter group.

Conclusions: In elderly Japanese subjects with low salt intake (<8.9 g/day), the addition of a low-dose diuretic (12.5 mg HCTZ) to ARB treatment causes significant reduction in srNa levels, which might affect blood osmolarity.

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Key Words: Angiotensin II receptor blocker; Diuretics; Hyponatremia; Salt intake
levels ≥8.0 mg/dl) and/or renal dysfunction (serum creatinine ≥2.0 mg/dl) were excluded.

Finally, 88 patients agreed to participate and their data were obtained after the start of the ARB+HCTZ treatment. Only 1 subject was categorized as having hyponatremia (<130 mEq/dl) at the end of the follow-up period. During the follow-up period, 5 subjects needed additional drugs for BP control, including newly starting a calcium-channel blocker in 4 patients,

| Table 1. Clinical Characteristics |
|----------------------------------|
| No. of patients (M/F) | 88 (52/26) |
| Age, years | 70±12 |
| Height, cm | 158.5±10.6 |
| Body weight, kg | 61.4±11.4 |
| Body mass index | 24.3±2.8 |
| Urine sodium output, mEq/L | 130.8±50.4 |
| Estimated salt intake, g/day | 13.5±5.0 |
| Healed myocardial infarction (%) | 5 (5.7) |
| Current or past smoker (%) | 33 (37.5) |
| Oral medications (%) |
| Calcium-channel blocker (%) | 65 (73.9) |
| β-blocker (%) | 27 (30.7) |
| α-blocker (%) | 4 (4.5) |
| for diabetes (%) | 13 (14.8) |
| for hyperuricemia (%) | 17 (19.3) |
| for dyslipidemia (%) | 32 (36.4) |

| Table 2. Changes in Variables From Time of Angiotensin II Receptor Blocker Treatment Alone to the Addition of 12.5 mg Hydrochlorothiazides in All Study Subjects (n=88) |
|----------------------------------|
| Before | After | P value |
| BUN (mg/dl) | 16.0±4.8 | 18.8±6.8 | <0.001 |
| Cr (mg/dl) | 0.87±0.24 | 0.96±0.33 | <0.001 |
| eGFR (ml · min⁻¹ · 1.73 m⁻²) | 63.4±15.2 | 58.5±16.8 | <0.001 |
| Na (mEq/L) | 141.6±1.8 | 140.8±2.8 | 0.003 |
| K (mEq/L) | 4.24±0.51 | 4.17±0.54 | 0.207 |
| Cl (mEq/L) | 104.1±2.6 | 102.9±4.5 | 0.008 |
| HbA1c (NGSP) (%) | 5.51±0.59 | 5.89±0.72 | 0.808 |
| UA (mg/dl) | 5.78±1.31 | 6.54±1.53 | <0.001 |
| LDL (mg/dl) | 99.9±27.4 | 101.4±30.4 | 0.617 |
| Systolic BP (mm Hg) | 148±18 | 131±14 | <0.001 |
| Diastolic BP (mm Hg) | 79±15 | 72±12 | <0.001 |
| Mean BP (mm Hg) | 102±13 | 92±10 | <0.001 |

BP, blood pressure; BUN, blood urea nitrogen; Cl, serum chloride; Cr, creatinine; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; K, serum potassium; LDL, low-density lipoprotein; Na, serum sodium; UA, uric acid.

Figure 1. Serum sodium levels at baseline (angiotensin II receptor blocker treatment) and after the add-on treatment of low-dose diuretic. Q1–5, quintile ranges of estimated sodium intake by the Kawasaki method; Q1–4: 28.1–9.3 g/day, lowest Q5: 8.9–4.3 g/day.
Serum levels of electrolytes (sodium, potassium and chloride), low-density lipoprotein (LDL) cholesterol, triglycerides, creatinine, uric acid, HbA1c, and blood glucose levels were determined by enzymatic methods. Urinary sodium and creatinine concentrations were measured using enzymatic methods.

Estimation of Glomerular Filtration Rate
Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation modified for the Japanese population: \( \{194 \times [\text{serum creatinine concentration}]^{–1.094} \times [\text{age}]^{–0.287} \times 0.739 \} \) for women.

Estimation of Daily Salt Intake
We calculated the daily salt intake (NaCl g/day) by the Kawasaki formula using second morning urine sample: \( 16.3 \times [\text{second morning urinary sodium concentration (mEq/L)/10} \times \text{estimated 24-h urinary creatinine excretion}]^{0.5} \times 55.8/1000 \). The formula used for estimating the 24-h urinary creatinine excretion from the demographic data was: \( 15.1 \times [\text{body weight (kg)} + 7.4 \times [\text{height (cm)} – 12.6 \times [\text{age (years)} – 79.9 \text{ for men, and } 8.6 \times \text{body weight (kg)} + 5.1 \times [\text{height (cm)} – 4.7 \times [\text{age (years)} – 75.0 \text{ for women.}}] \)

Study Protocol
After obtaining written informed consent, BP measurements and laboratory examinations were conducted before prescribing the combination of ARB plus 12.5 mg HCTZ. All patients were followed monthly at the outpatient department of Oshima Medical Center. After 6 months from starting the combination therapy, BP measurements and laboratory examinations were repeated.

In Japan, several combinations of ARB plus HCTZ 12.5 mg are available, the ARB component being losartan 50 mg, valsartan 80 mg, or telmisartan 40 or 80 mg. The choice of drug was left to the judgment of each physician (TS, YH, MN). The study protocol was approved by the Ethics Committee of Oshima Medical Center.

BP Measurement
BP was determined as the mean of 2 measurements obtained in an office setting by conventional cuff method using a mercury sphygmomanometer. The 2 measurements were performed with the subjects in the seated position after they had rested for at least 5 min.

Laboratory Measurements
Blood and urine samples were obtained after overnight fasting.

| Table 3. Clinical Characteristics and Changes in Variables From the Time of Angiotensin II Receptor Blocker Treatment to the Addition of 12.5 mg Hydrochlorothiazide Treatment Among Groups Categorized by Quintile Range of Salt Intake |
|---|---|---|---|---|
| **Age (years)** | **Q1 (28.1–17.2 g/day) (n=17)** | **Q2 (16.9–14.2 g/day) (n=17)** | **Q3 (14.1–12.3 g/day) (n=18)** |
| **Sex (male %)** | 64±3 | 72±2 | 67±3 |
| **BMI** | 24.2±1.8 | 24.9±3.9 | 24.1±1.7 |
| **Systolic BP (mmHg)** | 145±11 | 130±16 | 0.001 | 151±19 | 134±15 | 0.003 | 154±21 | 131±10 | 0.001 |
| **Diastolic BP (mmHg)** | 75±8 | 2.020 | 0.016 | 77±14 | 71±14 | 0.157 | 87±10 | 74±11 | <0.001 |
| **Mean BP (mmHg)** | 102±12 | 93±10 | 0.016 | 102±13 | 92±12 | 0.019 | 109±11 | 92±9 | <0.001 |
| **K (mEq/L)** | 4.26±0.38 | 4.22±0.34 | 0.598 | 4.19±0.52 | 4.14±0.47 | 0.615 | 4.13±0.38 | 4.09±0.55 | 0.751 |
| **Cl (mEq/L)** | 104.0±2.2 | 103.2±2.7 | 0.131 | 104.1±2.7 | 103.2±2.9 | 0.060 | 103.3±2.0 | 102.6±2.1 | 0.310 |
| **Cr (mg/dl)** | 72.3±14.1 | 70.9±17.7 | 0.602 | 65.2±13.7 | 61.8±12.7 | 0.104 | 64.7±19.1 | 62.4±14.9 | 0.405 |
| **eGFR (ml · min–1 · 1.73 m–2)** | 5.98±1.02 | 6.60±1.59 | 0.077 | 5.30±1.28 | 5.62±1.32 | 0.155 | 5.94±1.37 | 6.42±1.27 | 0.102 |
| **UA (mg/dl)** | 76±3 | 10/8 (55.6%) | 23.7±3.3 | 24.6±3.1 |
| **Sex (male %)** | 0.001 | 0.003 | 0.001 |
| **BMI** | 0.016 | 0.019 | 0.019 |
| **Systolic BP (mmHg)** | 0.598 | 0.615 | 0.751 |
| **Diastolic BP (mmHg)** | 0.131 | 0.060 | 0.310 |
| **Mean BP (mmHg)** | 0.016 | 0.019 | 0.019 |
| **K (mEq/L)** | 0.598 | 0.615 | 0.751 |
| **Cl (mEq/L)** | 0.131 | 0.060 | 0.310 |
| **Cr (mg/dl)** | 0.016 | 0.019 | 0.019 |
| **eGFR (ml · min–1 · 1.73 m–2)** | 0.598 | 0.615 | 0.751 |
| **UA (mg/dl)** | 0.016 | 0.019 | 0.019 |

Q1–5, quintile range of estimated sodium intake by the Kawasaki method; BP, blood pressure; Cl, serum chloride; Cr, creatinine; eGFR, estimated glomerular filtration rate; HCTZ, after addition of 12.5 mg hydrochlorothiazide; K, serum potassium; UA, uric acid.
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Statistical Analysis

Numerical values are expressed as mean±SD. Categorical data are expressed as percentages and were compared by chi-square test. The significance of the differences in the measurement values before and after the treatments was evaluated using a paired t-test. For assessment of the differences in the status of each variable among the groups, 1-way analysis of variance and the Kruskal-Wallis test were applied. For the assessment of significance of relationships among variables, univariate linear regression analysis was conducted. P-values less than 0.05 were considered to indicate a statistically significant difference. IBM SPSS software (SPSS 19; IBM Corporation, Chicago, IL, USA) was used to perform the statistical analyses.

Results

Clinical characteristics are shown in Table 1. Among the study subjects, 14.8% were prescribed medication for diabetes mellitus and 19.3% for hyperuricemia. The medications for diabetes and hyperuricemia were not changed during the follow-up period. The changes in the variables from the ARB treatment period to the combination therapy period are shown in Table 2. BP and srNa levels were significantly reduced, and the serum creatinine and uric acid levels were increased. LDL cholesterol, triglycerides and HbA1c levels were unchanged.

The estimated salt intake did not have a significant correlation with the changes in the srNa level from ARB treatment to the combination therapy. Thus, the patients were classified into quintile ranges of estimated salt intake: (Q1, 28.1–17.2 g/day; Q2, 16.9–14.2 g/day; Q3, 14.1–12.3 g/day; Q4, 12.2–9.3 g/day; Q5, 8.9–4.3 g/day). Although the srNa levels were not significantly changed by the addition of 12.5 mg HCTZ to ARB treatment among Q1–4, this add-on therapy significantly reduced srNa levels in Q5 (P=0.042; Figure 1). However, in the 1-way analysis of variance, the differences in the changes in srNa levels from ARB treatment to the combination therapy (the value of srNa levels before the add-on treatment minus the value after the add-on treatment) among these 5 groups were marginal (F-value 1.15, P=0.337). In addition, the differences in the srNa levels obtained at the end of the add-on treatment between subjects with and without strict salt restriction were not significant.

Table 3 shows clinical characteristics of the study participants and the changes in the other variables from the ARB treatment period to the add-on therapy period among the 5 groups. Age, sex, and body mass index were similar among the 5 groups. The add-on therapy was associated with a significant decrease in systolic BP and mean BP in all 5 groups, with no significant differences in the extent of the reduction of systolic and mean BPs among the 5 groups (data not shown). The diastolic BP remained unchanged in the Q1, Q2 and Q4 groups.

When patients were divided into 2 groups (ie, lowest Q5 vs. Q1–4), the reductions in srNa levels from ARB treatment to the combination therapy (12.5 mg HCTZ plus ARB) were significantly larger in the lowest group (Q5) than in the Q1–4 group (P=0.040; Figure 2). In contrast, the increases in the serum creatinine and uric acid levels were significantly larger in the former group than in the latter group (serum creatinine: P=0.001; serum uric acid: P=0.005; Figure 2).

Discussion

To the best of our knowledge, this is the first study to examine the association of dietary salt restriction with changes in srNa levels when switching from ARB treatment to combination therapy of 12.5 mg HCTZ plus the ARB. Byatt et al reported that the incidence rate of hyponatremia in HCTZ treatment as 11%,16 and the SHEP study,17 which used low-dose HCTZ, reported an incidence of 4.3%. However, in the SHEP study, 70% of study subjects were prescribed 25 mg, not 12.5 mg, HCTZ. The ARCH study, which examined the antihypertensive effect of 12.5 mg HCTZ plus 50 mg losartan for 1 year, reported that none of the study participants (n=651) had hyponatremia.18 Thus, hyponatremia is thought to be uncommon in 12.5 mg HCTZ treatment. Of all of the present study participants, only 1 patient demonstrated hyponatremia (srNa <130 mEq/dl). Approximately 50% of hyponatremia...
occurrence is observed within 6 months after starting the administration of HCTZ, and therefore, the finding of the present study is consistent with previous reports (ie, hyponatremia is not common under 12.5 mg HCTZ/ARB treatment).

Murai et al demonstrated that the frequency of use of diuretics in clinical practice (especially in combination with other antihypertensive drugs) has increased. Although low salt intake is a risk factor for the development of hyponatremia during HCTZ treatment, apparently no study has clearly evaluated the effect of low salt intake on the srNa levels under combined use of a low-dose diuretic (12.5 mg HCTZ) plus ARB. The guidelines for the management of hypertension by the Japanese Society of Hypertension 2009 (JSH2009) recommend a salt intake of 6 g/day or less, but Ohta et al reported that several subjects had difficulty in continuing salt restriction of less than 6 g/day. Thus, the extent of dietary salt restriction might differ among patients who are recommended to follow dietary salt restriction, and therefore, direct evaluation of the salt-restricted condition in each patient is proposed. The present study examined the dietary salt-restricted condition in each patient using urinary sodium excretion values (Kawasaki method). The add-on of low-dose HCTZ (12.5 mg) to the ARB treatment significantly reduced srNa levels in patients with a limited salt intake (<8.9 g/day), but not in those without such restriction.

The participants of the present study lived in a fishing village, and therefore most of them probably had a high dietary salt intake (mean daily salt intake 13.5 g/day). Low salt intake as defined (<8.9 g/day) in the present study might not represent strict restriction. However, the addition of a low-dose diuretic reduced the srNa levels in subjects with low salt intake. In the present study, there were no significant differences in the clinical characteristics of subjects with and without low salt intake. Therefore, when administration of a diuretic is planned, dietary salt intake and presence/absence of hyponatremia should be confirmed before the start of the diuretic.

In patients with heart failure, diuretic use at discharge has been associated with adverse outcomes. The risks of in-hospital death, follow-up mortality, and rehospitalization were increased by 19.5%, 10%, and 8%, respectively, for each 3 mmol/L decrease in srNa levels from those obtained on admission. These associations were observed even in the range of srNa levels not categorized as hyponatremia (ie, srNa levels of 130–140 mEq/dL).

Thus, low srNa levels might be harmful even without reaching the levels of hyponatremia. The increase in sodium excretion, together with diminished free-water excretion, is 1 of the major mechanisms of HCTZ-induced hyponatremia; blood osmolality is decreased in this situation. Usually, low-normal serum creatinine and hypouricemia are observed in patients with HCTZ-induced hyponatremia. In the present study, however, the significant elevations of the serum creatinine and uric acid levels following the addition of 12.5 mg of HCTZ to ARB treatment were larger in patients with low salt intake than in those without low salt intake. Therefore, patients with a low salt intake might remain in a dehydrated state to compensate for the hypo-osmolar state associated with the reduction in the srNa levels by the addition of a diuretic. Considering these findings, this significant reduction in srNa levels observed under the condition of limited salt intake might not be suitable for normal physiological conditions.

Study Limitations

The urinary analysis to estimate salt intake was conducted using the second urine sample collected in the morning, not the 24-h collected urine. In addition, interviews about diet content were conducted to estimate salt intake. Most of the subjects were elderly and had a history of high dietary salt intake because they lived in a fishing village. Further study is proposed to examine the association of salt intake with reduction of srNa levels caused by the addition of diuretic therapy in younger subjects and/or subjects with not such high dietary salt intakes (eg, subjects living in urban areas). The present study protocol did not examine the monthly changes in srNa levels after starting the combination therapy. Patients with various ARBs and various dosages of ARBs participated in the present study. Low salt intake is thought to potentiate the BP-lowering effect of diuretics, but in the present study, the extent of reduction of the systolic and mean BPs following the addition of diuretic therapy was similar among groups Q1–5; on the other hand, the add-on therapy failed to reduce the diastolic BP in Q1 (the group with the highest salt intake), Q2 or Q4 group. Thus, further study is proposed to examine the association of salt intake with the extent of BP reduction associated with combined use of a low-dose diuretic and an ARB.

Conclusion

Following the addition of a low-dose diuretic (12.5 mg HCTZ) to ARB treatment, hyponatremia is not common under the condition of low salt intake (<8.9 g/day). However, low salt intake causes significant reduction of the srNa levels, which might affect blood osmolality. Thus, confirmation of the salt intake condition is necessary before the addition of 12.5 mg of HCTZ to regular ARB treatment.

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