Original Article

Comparative study of therapeutic effects of short- and long-acting loop diuretics in outpatients with chronic heart failure (COLD-CHF)

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KEYWORDS
Chronic heart failure; Diuretic; Brain natriuretic peptide; Atrial natriuretic peptide

Summary
Background: Loop diuretics have two different classes with different duration of activity: short-acting such as furosemide (duration of activity, 6 h) and long-acting such as azosemide (duration of activity, 10–12 h). We conducted a multicenter, randomized, controlled trial in order to compare the therapeutic effects of azosemide, a long-acting loop diuretic, and furosemide, a short-acting one, on neurohumoral factors and cardiac function in outpatients with chronic heart failure (CHF).

Methods: We enrolled 98 patients with CHF who were receiving furosemide and an angiotensin-converting enzyme inhibitor, and they were randomly divided into furosemide (n=49) and azosemide (n=49) groups. The furosemide group continued furosemide at the same dosage, and the azosemide group switched from furosemide to azosemide. At baseline and after 3 months, we measured body weight, and levels of brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), norepinephrine, active renin, creatinine, blood urea nitrogen, sodium, potassium, and hematocrit. Chest X-ray and echocardiography were also performed.

Results: Body weight and plasma levels of BNP and ANP significantly decreased after 3 months in the azosemide group compared to the furosemide group. There were no significant differences in changes of levels of creatinine, blood urea nitrogen, sodium, potassium, hematocrit, norepinephrine, and active renin after 3 months between the furosemide and azosemide groups.

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Short- and long-acting diuretics in CHF

Echocardiography and chest X-ray did not demonstrate significant differences between the two groups.

Conclusions: Long-acting azosemide is suggested to be useful for the improvement of neurohumoral factors compared with short-acting furosemide in patients with CHF.
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Introduction

Heart failure is a major and growing public health problem, and the number of heart failure deaths has increased steadily despite advances in treatment [1]. Diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in patients with chronic heart failure (CHF) [2–4]. Loop diuretics with strong diuretic effects are essential for the treatment of pulmonary congestion and symptoms in heart failure patients [1]. The loop diuretics are categorized into short- and long-acting groups based on their duration of action. Furosemide with rapid action is a potent diuretic representing the short-acting group, while azosemide with a mild and long-lasting effect is representative of the long-acting group [5].

Despite their hypotensive effects, short-acting calcium channel blockers were reported to increase mortality in patients with cardiovascular disease, while long-acting calcium channel blockers were not associated with increased mortality in hypertensive patients [6,7]. This hypothesis can also be applied theoretically to diuretics with different durations of action in patients with CHF. Azosemide, a long-acting loop diuretic, was associated with a better outcome in Dahl rat heart-failure models compared with short-acting furosemide, partly through attenuation of the reflex increase in cardiac sympathetic neuronal activity caused by the development of heart failure [8]. Furthermore, the comparative effects of long-acting azosemide and short-acting furosemide on neurohumoral factors, and the usefulness of azosemide for improving quality of life were shown in a clinical study [9,10]. However, these studies were only performed in a small number of patients in a single hospital, and thus the usefulness of long-acting diuretics has not yet been validated. Therefore, we conducted a multicenter randomized controlled trial, and compared the effects of azosemide on neurohumoral factors and cardiac function to those of furosemide in outpatients with CHF of New York Heart Association (NYHA) class I–III.

Methods

Patients

We enrolled 98 consecutive CHF outpatients with NYHA class I–III whose brain natriuretic peptide (BNP) level was greater than 20 pg/ml, who had been receiving an angiotensin-converting enzyme (ACE) inhibitor and furosemide for at least 1 month and were in a stable condition. They were not administered any angiotensin II type 1 receptor blocker (ARB). The diagnosis of heart failure was defined by symptoms, clinical signs, and BNP levels more than 100 pg/ml before medication [11].

Study design

This randomized multicenter clinical trial was conducted at 16 hospitals in Japan from October, 2005 to January, 2008. The patients were randomly divided into furosemide and azosemide groups by an envelope method. The furosemide group was assigned to continue receiving furosemide, and the azosemide group was assigned to switch from furosemide to azosemide. Regarding the doses of both drugs, 20 and 40 mg furosemide was equivalent to approximately 30 and 60 mg azosemide, respectively, based on the results of a clinical pharmacology study [5]. Examinations were conducted 3 months after registration, and all clinical parameters were examined before and 3 months after assignment. Readers of chest X-ray and echocardiography were blinded to the investigation in the treatment allocation, although the grouping was open to physicians and patients. Concomitant ACE inhibitors already being used at enrollment were continued as prescribed. Other drugs were also allowed to continue without making further changes after registration. Cases requiring any changes in medication, including other heart failure drugs, were defined as dropouts.

The study design complied with the Declaration of Helsinki and was unanimously approved by the Ethics Committee of Kagoshima University. Written informed consent was obtained before enrolment from all of the patients who participated in the present study.

Physical examination and chest X-ray

The NYHA functional class, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and cardiothoracic ratio (CTR) on chest radiography were determined before and 3 months after commencing the study.

Laboratory examinations

A fasting blood sample was taken in the morning. The plasma levels of BNP, atrial natriuretic peptide (ANP), norepinephrine (NE), and renin activity, the serum levels of creatinine, blood urea nitrogen, sodium, potassium, and chloride, and hematocrit were measured before and 3 months after assignment.

Echocardiography

Cardiac function was evaluated by echocardiography before and 3 months after the start of the clinical trial. Standard two-dimensional and Doppler echocardiographic
examinations were performed in all subjects using 1- to 5-MHz phased array transducers and commercially available scanners [12]. Left ventricular systolic dimension (LVDs) and diastolic dimension (LVDd), and left atrial dimension (LAD) were determined. Left ventricular ejection fraction (LVEF) was obtained by modified bivale Simpson’s method from apical 2- and 4-chamber views. LV mass was calculated by the American Society of Echocardiography-recommended formula [13]: LV mass (g) = 0.8 × [(1.04[(LVDd + posterior wall thickness + interventricular septum thickness)]2 – (LVDd)2)] + 0.6 g. LV mass was divided by body surface area to obtain LV mass index (LVMI).

Doppler time intervals were measured from the left ventricular (LV) inflow and outflow velocities, and Tei index was determined as shown in Fig. 1. Interval ‘‘a’’ was measured from the cessation of LV inflow to the onset of the next inflow. Interval ‘‘b’’, ejection time, was measured from the onset of LV outflow velocity to its cessation. LV isovolumic relaxation time (IRT) was calculated by subtracting interval ‘‘d’’, between the R wave on the electrocardiogram and the cessation of LV ejection flow, from interval ‘‘c’’, between the R wave and the onset of LV inflow. LV isovolumic contraction time (ICT) was obtained by subtracting IRT from (a – b). All measurements were performed from three consecutive beats, and average values were determined. LV Tei index, defined as the sum of the isovolumic contraction and relaxation times divided by the ejection time, was calculated as (a – b)/b [14–16]. In addition, right ventricular (RV) Tei index was also calculated from Doppler time intervals, which were determined from RV inflow and RV outflow velocities. LV and RV Tei indices represent a composite of systolic and diastolic function of the LV and RV, respectively.

Statistical analysis

Values are expressed as mean ± SD, except for ANP and BNP which are shown as median (25th and 75th percentiles). Paired t-test and χ2 test were used for intra-group comparison (prior to and 3 months after initiation of the trial), and unpaired t-test was performed for inter-group comparison (comparison of changes in parameters after administration between furosemide and azosemide groups). Non-parametric Mann—Whitney U test was used for non-normally distributed variables, such as ANP and BNP. A p-value less than 0.05 was considered to indicate significant difference.
Table 1  Patient characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Furosemide group (n = 49)</th>
<th>Azosemide group (n = 48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>75.7 ± 7.9</td>
<td>75.8 ± 9.6</td>
<td>0.957</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (61.2%)</td>
<td>21 (43.7%)</td>
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</tr>
<tr>
<td>Female</td>
<td>19 (38.8%)</td>
<td>27 (56.3%)</td>
<td></td>
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<tr>
<td>Body weight (kg)</td>
<td>53.7 ± 11.1</td>
<td>56.3 ± 12.1</td>
<td>0.267</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.0 ± 9.6</td>
<td>154.5 ± 11.3</td>
<td>0.807</td>
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<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>14</td>
<td>14</td>
<td>0.882</td>
</tr>
<tr>
<td>Class II</td>
<td>33</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CTR (%)</td>
<td>54.6 ± 5.5</td>
<td>55.7 ± 6.6</td>
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<tr>
<td>LVEF (%)</td>
<td>58.0 ± 16.2</td>
<td>59.8 ± 13.7</td>
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<tr>
<td>LVDD (mm)</td>
<td>51.2 ± 7.9</td>
<td>48.2 ± 9.7</td>
<td>0.092</td>
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<tr>
<td>LVDS (mm)</td>
<td>35.2 ± 9.7</td>
<td>33.3 ± 8.0</td>
<td>0.314</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>42.7 ± 8.1</td>
<td>41.9 ± 7.1</td>
<td>0.621</td>
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<tr>
<td>LVMi (g/m²)</td>
<td>137.1 ± 35.5</td>
<td>130.1 ± 43.5</td>
<td>0.392</td>
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<tr>
<td>LV Tei index</td>
<td>0.49 ± 0.20</td>
<td>0.46 ± 0.16</td>
<td>0.369</td>
</tr>
<tr>
<td>RV Tei index</td>
<td>0.33 ± 0.13</td>
<td>0.32 ± 0.13</td>
<td>0.687</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>90.2 (51.2, 160.0)</td>
<td>102.5 (58.7, 211.5)</td>
<td>0.218</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>31.0 (21.0, 53.0)</td>
<td>48.0 (28.0, 61.0)</td>
<td>0.139</td>
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</tbody>
</table>

Etiology of heart failure

<table>
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<tr>
<th></th>
<th>Furosemide group (n = 49)</th>
<th>Azosemide group (n = 48)</th>
<th>p-value</th>
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<tr>
<td>Valvular disease</td>
<td>29</td>
<td>26</td>
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<tr>
<td>Ischemic heart disease</td>
<td>12</td>
<td>13</td>
<td>0.966</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
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<tr>
<td>Enalapril</td>
<td>29</td>
<td>25</td>
<td></td>
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<tr>
<td>Imidapril</td>
<td>20</td>
<td>21</td>
<td>0.236</td>
</tr>
<tr>
<td>Delapril</td>
<td>0</td>
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</tr>
<tr>
<td>β blocker</td>
<td>9</td>
<td>9</td>
<td>0.832</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>7</td>
<td>8</td>
<td>0.785</td>
</tr>
<tr>
<td>Statin</td>
<td>10</td>
<td>12</td>
<td>0.634</td>
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<tr>
<td>Digitalis</td>
<td>12</td>
<td>13</td>
<td>0.819</td>
</tr>
<tr>
<td>Nitrate</td>
<td>11</td>
<td>13</td>
<td>0.644</td>
</tr>
</tbody>
</table>

Values are mean ± SD except for ANP and BNP which are shown as median (25th and 75th percentiles); NYHA, New York Heart Association; CTR, cardiothoracic ratio; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; LVDS, left ventricular end-systolic dimension; LAD, left atrial dimension; LVMi, left ventricular mass index; LV, left ventricular; RV, right ventricular; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; ACE, angiotensin converting enzyme; NS, not significant.

Neurohumoral factors

With regard to plasma levels of BNP and ANP, the azosemide group showed a decline in these two factors whereas the furosemide group showed an increase in both parameters, demonstrating significant differences in the changes in these two markers between the two groups (p < 0.05, Fig. 3A and B). In contrast, there were no significant differences in changes of plasma levels of norepinephrine and renin activity after 3 months between the furosemide and azosemide groups (Table 2).

Echocardiography

LV Tei index tended to increase after 3 months in the furosemide group, while it decreased in the azosemide group; however, there was no significant difference in the changes between the groups (Fig. 4A). Although RV Tei index significantly increased after 3 months in the furosemide group, there was no significant difference in changes in RV Tei index between the groups (Fig. 4B). There were no significant differences in changes in LVDD, LVDS, LVEF, LAD, and LVMi after 3 months between the furosemide and azosemide groups.

Discussion

Loop diuretics are regarded as suitable for improving pulmonary congestion and heart failure symptoms by reducing preload, as described in the guidelines for treatment of CHF [17]. Loop diuretics have two different classes with different duration of activity: short-acting such as furosemide (duration of activity, 6 h) and long-acting such as azosemide (duration of activity, 10—12 h) [5]. In the present study,
Table 2 Changes in blood pressure, PRA, NE, BUN, Cr, K, Na, Cl, and hematocrit.

<table>
<thead>
<tr>
<th></th>
<th>Furosemide group (n = 49)</th>
<th>Azosemide group (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>136.1 ± 26.2</td>
<td>135.3 ± 27.9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71.9 ± 14.4</td>
<td>71.5 ± 12.0</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>4.3 ± 5.4</td>
<td>4.5 ± 6.1</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>513.0 ± 280.3</td>
<td>472.2 ± 267.6</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>23.0 ± 8.2</td>
<td>21.1 ± 9.0</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.97 ± 0.42</td>
<td>1.03 ± 0.33</td>
</tr>
<tr>
<td>K (mmol)</td>
<td>4.3 ± 0.5</td>
<td>4.4 ± 0.5</td>
</tr>
<tr>
<td>Na (mmol)</td>
<td>142.0 ± 3.5</td>
<td>142.8 ± 3.3</td>
</tr>
<tr>
<td>Cl (mmol)</td>
<td>106.6 ± 12.6</td>
<td>104.4 ± 3.7</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>37.2 ± 5.7</td>
<td>36.1 ± 5.4</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; PRA, plasma renin activity; NE, norepinephrine; BUN, blood urea nitrogen; Cr, creatine; Ht, hematocrit.

* p < 0.05 vs baseline in furosemide group.

Figure 3 Changes in brain natriuretic peptide (BNP) (A) and atrial natriuretic peptide (ANP) (B) after 3 months. White bars are furosemide group; black bars are azosemide group.

Figure 4 Changes in left ventricular (LV) Tei index (A) and right ventricular (RV) Tei index (B) after 3 months. White bars are furosemide group; black bars are azosemide group. * p < 0.05 for comparison between baseline and after 3 months.

we compared the effect on neurohumoral factors between furosemide and azosemide, and found that long-acting azosemide significantly decreased plasma BNP and ANP levels compared with short-acting furosemide.

ANP and BNP are secreted mainly from the atria and ventricles, respectively, and these markers are predictors of LV dysfunction. The plasma ANP and BNP levels are considered a particularly useful predictive biomarker for prognosis and cardiovascular events in patients with CHF [18–20] and acute myocardial infarction [21]. In the SAVE study, where neurohumoral factors were measured 12 days after myocardial infarction in 534 patients, multivariate analysis revealed that only plasma ANP level and plasma renin activity on day 12 after disease onset were associated with outcome in patients with acute myocardial infarction [22]. In the Val-HeFT study, plasma levels of norepinephrine, aldosterone, and BNP were measured in 4300 patients with moderate to severe heart failure, and the plasma BNP level showed the greatest prognostic value [23]. In the present study, these parameters significantly decreased in the azosemide group compared to those in the furosemide group, suggesting that long-acting diuretics may be useful for improving cardiac function and prognosis in CHF.

McCurley et al. conducted a placebo-controlled comparative study to investigate the effect of furosemide on progression of LV dysfunction in a heart failure model, and reported that furosemide significantly accelerated the progression of LV systolic dysfunction [24]. In addition, Starklint et al. reported that administration of furosemide did not induce any significant change in plasma ANP and BNP levels in CHF patients [25]. The present study also demonstrated that neurohumoral factors and cardiac function assessed by echocardiography were not fully improved by furosemide. Several investigators reported that the furosemide causes excessive volume loss and electrolyte disturbances due to its strong and rapid diuretic effect, and the response to the rapid volume reduction may lead to activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, resulting in increased plasma ANP and BNP levels [26,27], although
we failed to show the differences in responses of symp-
pathetic nerve activity and electrolytes between the two
groups. It is likely that these undesirable effects of rapid
diuretics might disturb the improvement in cardiac function
expected with furosemide. In contrast, azosemide showed
significantly decreased plasma BNP and ANP levels compared
to furosemide in the present study. This result suggests
that the benefit of azosemide is associated with its mild
and long-acting diuretic effect without inducing unfavorable
responses, resulting in high usefulness for treatment of CHF.

Limitations

We did not evaluate the effect of diuretics on the prognosis
of heart failure. Further clinical examinations are needed
to examine the different outcomes in CHF patients treated
with long- and short-acting diuretics. Comparison of the
effect of furosemide and azosemide on the prognosis in
CHF patients is currently underway in a prospective mul-
ticenter study [28]. The relatively low prescription rate of
β-blockers, and the high cardiac valvular disease preva-
lence, which is estimated to be 50%, might make our study
difficult to apply to general heart failure.

Conclusion

Long-acting azosemide, with coadministration of an ACE
inhibitor, is suggested to be more useful than short-acting
furosemide in improving neurohumoral factors in patients
with CHF.

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Conflict of interest

None declared.

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