Tolerability and Safety of a Calcium Channel Blocker in Comparison with a Diuretic in the Treatment of Elderly Patients with Hypertension: Secondary Analysis of the NICS-EH

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A randomized prospective controlled study, the National Interventional Cooperative Study in Elderly Hypertensives (NICS-EH), previously demonstrated that the preventive effect of the long-acting calcium channel blocker nicardipine on the cardiovascular endpoint was similar to that of the diuretic, trichlormethiazide. The present report is a sub-analysis in which we compare the tolerability and safety of the calcium channel blocker with that of a diuretic in the long-term treatment of elderly hypertensives. A total of 429 elderly patients with hypertension were assigned to the nicardipine group or the diuretic group by the double-dummy method and were followed up for 5 years. Two hundred four patients in the nicardipine group and 210 patients in the diuretic group were analyzed. The incidences of fatal and nonfatal cardiovascular (CV) events in the two groups were comparable, and there was no significant difference in the cumulative event-free rate. However, the total incidence of adverse reactions, including non-CV events and unfavorable BP changes, was 31 cases (15.2%) in the nicardipine group, which was significantly lower than the 47 cases (22.4%) in the diuretic group (log-rank: p=0.026, G. Wilcoxon: p=0.01). The total number of medical endpoints, including CV events, the withdrawal of the patient from the study, was 52 (25.5%) in the nicardipine group, which was significantly lower than the 65 (31.0%) in the diuretic group (log-rank: p=0.078, G. Wilcoxon: p=0.044). It was concluded that sustained-release nicardipine is better tolerated, as it exhibits a lower incidence of medical-related withdrawals such as adverse drug reactions, non-cardiovascular events and unfavorable BP responses during the treatment. (Hypertens Res 2001; 24: 475–480)

Key Words: elderly, calcium channel blocker, diuretics, randomized prospective trial

Introduction

The clinical use of diuretics has been declining in the past two decades despite much evidence in support of their effectiveness (1–3) and despite the recommendation of the WHO/ISH (4) or JNC-VI guidelines (5). The usage of calcium channel blockers, in contrast, has rapidly been increasing.
Table 1. Incidence of Non-Cardiovascular Event, Adverse Reactions and Unfavorable BP Changes

<table>
<thead>
<tr>
<th></th>
<th>Nicardipine group</th>
<th>Diuretic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fainting, fatigue</td>
<td>6 (2.9%)</td>
<td>9 (4.3%)</td>
</tr>
<tr>
<td>Numbness</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>GI symptom</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Eruption</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>14 (6.9%)</td>
<td>16 (7.6%)</td>
</tr>
<tr>
<td>events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>New onset of diabetes</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Dementia, depression</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Osteo-arthritis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lung disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Colon polyps</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Unfavorable BP changes</td>
<td>11 (5.4%)</td>
<td>22 (10.5%)</td>
</tr>
<tr>
<td>Excessive BP elevation</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Excessive BP reduction</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>31 (15.2%)</td>
<td>47 (22.4%)</td>
</tr>
</tbody>
</table>

Subjects and Methods

The details of the design and method of the trial (8) were previously reported. In brief, hypertensive elderly patients over 60 years old were recruited for the study. The eligible sitting blood pressure (BP) of the patients ranged between 160 and 220 mmHg for systolic and below 115 mmHg for diastolic. Patients with secondary hypertension or cardiovascular complications were excluded from the study. Patients were randomly assigned to two groups by the double-dummy method and were followed up for 5 years. One group took a 20 mg nicardipine hydrochloride retard capsule twice a day (N), and the other took 2 mg of trichlormethiazide once a day (T). When BP control was considered to be insufficient, the dose was adjusted upward to a maximum of twice the initial dose.

The primary endpoint was a CV event, such as stroke, myocardial infarction, congestive heart failure, renal insufficiency, or death. The secondary endpoint was defined as a withdrawal due to an adverse reaction, a non-cardiovascular event or excessively increased or decreased blood pressure during the follow-up period. Informed consent was obtained from all participants.

In the present sub-analysis, the incidence of secondary endpoints was compared between the two groups, and the cumulative event-free rates were calculated using the Kaplan-Meier method for each group. A comparison of the cumulative event-free rates was then carried out between the two groups using the log-rank test and generalized (G) Wilcoxon test. Risk ratios were calculated with proportional hazard regression analysis.

Results

A total of 429 patients were randomly assigned to the nicardipine group (215) and the diuretic group (214). Twelve patients who did not return to the hospital after the observation period and 3 patients who were disqualified because of their age and primary disease were withdrawn from the follow-up study. Analyzable data was collected on a total of 414 patients, including 204 in the nicardipine group and 210 in the diuretic group. In terms of clinical background, no significant differences between the two groups were observed except for the high proportion of women in the nicardipine group compared with the diuretic group (p = 0.003).

BP was reduced from 172±13/94±10 mmHg to 152±16/85±9 mmHg in the nicardipine group and from 173±11/93±10 mmHg to 153±17/85±10 in the diuretic group at 8 weeks. At 240 weeks, BP fell to 147±15/81±8 mmHg and 147±16/79±9 mmHg in the two groups, respectively.

Major CV Endpoints (Primary Endpoints)

The incidence of fatal and non-fatal major CV events was similar in the two groups: 21 (10.3%) in the nicardipine group and 18 (8.6%) in the diuretic group (p = 0.923; log-rank, p = 0.785: G. Wilcoxon). After adjusting for gender and age, the risk ratio in the nicardipine group was 0.973 (95%CI: 0.514–1.839, p = 0.932).

Secondary Endpoints (Table 1, Fig.1)

Withdrawals due to Adverse Reactions

Withdrawals from the study due to adverse reactions occurred in 6 patients (2.9%) in the nicardipine group and in 9 patients (4.3%) in the diuretic group. After adjusting for gender and age, the risk ratio for the nicardipine group was
Fig. 1. Relative risk of nisardipine compared to trichlormethiazide. Odds ratios, plotted with 95% CI on a log scale co-
variates. *: gender and age, **: gender, age and systolic BP, multiplicity is ignored.

Fig. 2. Cumulative medical event-free curve (cardiovascular events were excluded).

0.677 (95% CI: 0.24–1.92, p = 0.464).

Withdrawal due to Non-Cardiovascular Events
Non-cardiovascular events requiring withdrawal from the study, such as cancer, a new onset of diabetes mellitus, de-
mentia, osteo-arthritis, infection, lung disease, and colon polyps, were observed in 14 patients (6.9%) in the nisardipine
group and in 16 patients (7.6%) in the diuretic group. Af-
ter adjusting for gender and age, the risk ratio for the
nisardipine group was 0.75 (95% CI: 0.36–1.54, p = 0.433).

Withdrawal due to Unfavorable BP Changes
Despite the doubling of the antihypertensive agent dose, 8
patients in the nisardipine group and 16 patients in the di-
uretic group were withdrawn from the study due to an eleva-
tion of BP to over 200/100 mmHg. In addition, 3 patients in
the nisardipine group and 6 in the diuretic group were with-
drawn from the study due to an excessive reduction in BP
during the follow-up period. In total, 11 patients (5.4%) in
the nisardipine group and 22 patients (10.5%) in the diuretic
group were withdrawn from the trial because of unfavorable
BP changes. After adjusting for gender, age and systolic BP,
the risk ratio for the nisardipine group was 0.45 (95% CI: 0.22–0.95, p = 0.035).

The total number of withdrawals due to adverse reactions,
non-CV events and unfavorable BP changes was 31 in the
nisardipine group (15.2%) and 47 in the diuretic group
(22.4%). The cumulative medical-event-free rates, excluding
CV events, were significantly lower in the nisardipine group
than in the diuretic group (p = 0.026: log rank, p = 0.010: G.
Wilcoxon, Fig. 2). After adjusting for gender, age and sys-
tolic BP, the risk ratio for the nisardipine group was 0.605
(95% CI: 0.382–0.957, p = 0.032).

Endpoints, including major CV and non-CV events, ad-
verse effects and unfavorable BP changes, occurred in 52 pa-
tients (25.5%) in the nisardipine group and 65 (31.0%) in the
diuretic group (p = 0.078). After adjusting for age, gender
and systolic BP, the risk ratio for the nisardipine group was
0.71 (95% CI: 0.491–1.027, p = 0.069, Fig. 1).

The time interval before a withdrawal occurred due to any
medical endpoint appeared to be shorter in the diuretic group
than in the nisardipine group. A comparison of the cumula-
tive event-free rates between the two groups was therefore
conducted using G. Wilcoxon, which is able to detect the
difference between the event-free rate in the two groups at
an earlier point. As shown in Figs. 2 and 3, the p-value was
less than 0.05 in both the comparison of the incidence of sec-
ondary endpoints and the comparison of all medical events
involving CV events between the two groups.

This finding indicates that the incidence of earlier with-
drawal due to a secondary endpoint was significantly higher
in the diuretic group than the nisardipine group.

Laboratory Test Data
Figure 4 shows a comparison between the two groups of
changes in the laboratory test values that occurred during the
trial. The changes in serum sodium and uric acid in the
diuretic group were significantly larger than in the nisardipine
group. The changes in blood urea nitrogen and glucose were
also significantly larger in the diuretic group than in the
nisardipine group. Significantly more patients in the diuretic
group showed abnormal blood urea nitrogen levels higher than 30 mg/dl ($p = 0.033$).

**Discussion**

The BP-lowering effect of diuretics and their consequent preventive effect for cardiovascular complications have been confirmed by SHEP (1) and other trials (2, 3, 11, 12). It has also been reported that elderly hypertensives respond better to diuretics than do younger patients (13). Despite the apparent usefulness of diuretics, the rate at which they are prescribed has been decreasing worldwide, and the use of calcium channel blockers and angiotensin-converting enzyme inhibitors has been rapidly increasing. Although the preventive effects of calcium channel blockers for the cardiovascular complications have been demonstrated by the Syst-Eur (6), Syst-China (7) and STONE (14) trials, randomized clinical trials that compare the long-term effects of calcium channel blockers with those of diuretics had been lacking until the recent publications of NICHES-EH (8), INSIGHT (10) and NORDIL (15). The NICS-EH trial (8) first demonstrated that a calcium channel blocker could be as useful as a diuretic in the prevention of CV events in elderly with hypertension. In the present sub-analysis of the NICS-EH trial, the withdrawal of patients from the study due to non-cardiovascular events, adverse reactions, and unfavorable BP changes were less frequent in the nitriddipine group than in the diuretic group. This finding suggests that calcium channel blockers are superior to diuretics in terms of tolerability and safety.

The high incidence of intolerability and the negative metabolic effects have been a great drawback of diuretics in clinical practice. The prevalence of any specified problem characterized as intolerable in the diuretic group was 28.1%, which is greater than that of 20.8% in the placebo group in the SHEP trial (1). Recently, Franse et al. (16) conducted a secondary analysis of SHEP and reported that after a 1 year follow-up period, 7.2% of the participants randomized to active treatment had a serum potassium level of less than 3.5 mmol/l, compared with 1% of the participants randomized to placebo. More importantly, those researchers found the risk of cardiovascular events and of coronary events to be 51% and 55% lower, respectively, among those who had normal serum potassium levels than those who experienced hypokalemia within the active treatment group ($p < 0.059$). This finding suggested that hypokalemia might offset the cardiovascular benefits obtained using thiazide.

SHEP (1) also showed that the increases in serum uric acid, serum glucose and serum cholesterol in the diuretic group were higher than those in the placebo group. The development of hyperuricemia and diabetes requires supplemental anti-hyperuricemic drugs or an anti-diabetic regimen. In terms of medical economy, the long-term prescription of diuretics does not always produce benefits that outweigh the costs.

In contrast, the Syst-Eur trial (6), which compared the long-term cardioprotective effects of calcium channel blockers with those of a placebo, showed that the rates of intercurrent diseases of non-cardiovascular origin that led to either admission to hospital, withdrawal from double-blind treatment, or supervised open follow-up were similar in both groups.

In the INSIGHT trial (10), of the patients assigned to co-
amilozide, 60% were well controlled with mono-therapy, but they also showed a higher incidence of metabolic disorders such as hypokalemia, hypernatremia, hyperuricemia, hyperglycemia, and renal impairment than did the patients on nifedipine. Thus, the trial showed that the incidence of metabolic adverse effects increased in the process of up-dosing the diuretics to achieve the optimal blood pressure level. Trials (1–3, 6, 8, 10) suggested that the preventive effects of diuretics on cardiovascular complications are comparable with those of calcium channel blockers unless they have negative metabolic adverse effects. However, supplemental administrations of potassium or antiuricemic agents are frequently required for patients treated with diuretics in clinical practice.

The incidence of both non-fatal congestive heart failure and peripheral edema in the nifedipine group was significantly higher in the INSIGHT trial. In the present study, the incidence of congestive heart failure and peripheral edema was very low (1 case) in the nifedipine group. Although the reason for the occurrence of these adverse effects remains unclear, the different clinical backgrounds of the subjects may be influential, because high risk patients with at least one additional cardiovascular risk were recruited in the INSIGHT trial (10), while only patients with few complications were eligible in the NICS-EH (8).

The advantage of a long-acting calcium channel blocker is an intense and persistent BP lowering effect as shown in the INSIGHT trial (10), in which 69% of patients attained a BP level close to 138/82 mmHg through nifedipine monotherapy. Our previous study (17) showed that the BP reduction caused by calcium channel blockers was not age-dependent,
but did correlate with the pretreatment BP level. Systolic BP tends to increase with advancing age; the apparently greater antihypertensive effect of calcium channel blockers in elderly patients may be related with this characteristically higher systolic BP. Clinical trials (3, 7, 8) conducted in Japan and China revealed that the incidence of stroke in hypertensive patients living in north Asia was relatively higher than the incidence of coronary heart disease. For example, the ratio of stroke to myocardial infarction in the NICS-EH study (8) was 4, whereas this ratio ranged from 0.8 to 1.3 in the trial conducted in Western countries (1, 6, 11, 12).

Although a criticism of calcium channel blockers reappeared in a recent meta-analysis conducted by Pahor et al. (18), there are some differences in the assessment of the calcium channel blocker with the findings of the Blood Pressure Lowering Treatment Trialists’ Collaboration (19), probably due to the selection of clinical trials. Recent reliable clinical trials (6, 7) denied the possibility of the cardio-toxicity and bleeding tendency caused by calcium channel blocker as described by Furbod et al. (20–22).

The findings of the present study support the experience noted in clinical practice that calcium channel blockers can be used in long-term hypertension treatments without serious adverse effects.

NICS-EH Study Group

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