The Effects of Low-dose Bisoprolol on the Renin-Angiotensin-Aldosterone System and Ventricular Remodelling

X Zhong, C Zhao, Y Zhang, Y Li, H Zhang, R He

ABSTRACT

Objective: To explore the effects of low-dose bisoprolol on the renin-angiotensin-aldosterone system (RAAS) and ventricular remodelling.

Methods: Eighty patients who were initially diagnosed with hypertension and left ventricular hypertrophy were investigated for the renin, angiotensin II and aldosterone levels in plasma and the thickness of the left ventricular posterior wall, interventricular septum and left ventricular mass index after 24 weeks of treatment with oral bisoprolol. The results were then compared with the readings before treatment.

Results: After treatment, all of the indices mentioned above were compared with those before treatment and were found to be significantly lower. The differences were significant (p < 0.05).

Conclusion: Bisoprolol can inhibit the RAAS and reverse ventricular remodelling.

Keywords: Bisoprolol, hypertension, renin-angiotensin-aldosterone system, ventricular remodelling

Efectos del bisoprolol en dosis bajas sobre el sistema renina-angiotensina-aldosterona y la remodelación ventricular

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RESUMEN

Objetivo: Explorar los efectos del bisoprolol en bajas dosis sobre el sistema renina-angiotensina-aldosterona (SRAA) y la remodelación ventricular.

Métodos: Ochenta pacientes que inicialmente fueron diagnosticados con hipertensión e hiperтроfia ventricular izquierda, fueron sometidos a investigaciones para determinar los niveles de renina, angiotensina II, y aldosterona en plasma, así como el espesor de la pared posterior del ventrículo izquierdo, el septo interventricular, y el índice de masa ventricular izquierda, después de 24 semanas de tratamiento con bisoprolol oral. Los resultados fueron entonces comparados con las lecturas antes del tratamiento.

Resultados: Tras el tratamiento, todos los índices arriba mencionados, fueron comparados con los índices anteriores al tratamiento, y se halló que eran significativamente más bajos. Las diferencias fueron significativas (p < 0.05).

Conclusión: El bisoprolol puede inhibir el SRAA y revertir la remodelación ventricular.

Palabras claves: Bisoprolol, hipertensión, sistema renina-angiotensina-aldosterona, remodelación ventricular
INTRODUCTION
Taking into account the high rates of hypertension and cardiovascular disease (1), it is important to choose antihypertensive drugs which will have better patient compliance and fewer adverse reactions and which will not only smoothly lower blood pressure but also improve prognosis. Estimates of risk reduction from meta-analyses and systematic reviews of β-blockers range from a 16% reduction in mortality in patients with diabetes mellitus to a 35% reduction in mortality primarily from arrhythmia-associated sudden death (2–4). β-blockers are important in the treatment for heart failure, atrial fibrillation and hypertension (5–7). Bisoprolol is a highly selective β1-blocker. This study investigated the effects of small doses of bisoprolol as an antihypertensive and the effect on the renin-angiotensin-aldosterone system (RAAS) and ventricular remodelling.

SUBJECTS AND METHODS
Eighty hypertensive patients who were treated at the Department of Cardiology of the Huaihe Hospital of Henan University in 2015 were selected. All of them satisfied the hypertension diagnostic criteria of the 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Echocardiography showed left ventricular hypertrophy (LVH), with no previous drug treatment (antihypertensive). There were 35 men and 45 women, with an average age of 52.3 years. Patients with secondary hypertension, significant cardiac insufficiency, pregnancy, lactation, a history of chronic obstructive pulmonary disease, a heart rate of < 60 beats/minute, sinoatrial block or second-degree atrioventricular block type II or above, peripheral vascular disease, severe liver and kidney dysfunction or other organic heart disease were excluded.

Measurements and criteria of blood pressure
A standard mercury sphygmomanometer was used to measure sitting blood pressure of the right upper limb after patients had rested for 15 minutes. Korotkoff I was taken as systolic blood pressure (SBP) and the reading of Korotkoff V taken as diastolic blood pressure (DBP). This was continuously measured three times each day at intervals of 30 seconds. The average of the three results was taken as the standard blood pressure of the day.

Cardiac echocardiography
A VIVID-7 type ultrasonic diagnostic apparatus produced by GE Healthcare was used to measure the thickness of the left ventricular long axis of the left ventricular posterior wall (LVPW) and interventricular septum (IVS), and left ventricular end-diastolic diameter. The left ventricular mass index (LVMI) was calculated according to the Devereux formula. IVS > 12 mm or left ventricular mass weight (LVMW) (male) > 12 g/m², LVMW (female) > 120 g/m² were all considered as LVH.

Determination of renin, angiotensin and aldosterone
Fasting venous blood was placed in a 2 mL anticoagulant tube, which contained 30 μL 10% EDTA-2Na, mixed with 40 μL aprotinin, at 4°C, 3000 r/minute and centrifuged for 10 minutes. Plasma was separated, saved and stored at -20°C. Renin (Ren), angiotensin II (Ang II) and aldosterone (Ald) levels were measured by radioimmunoassay (RIA) serum (RIA kit purchased from the RIA Technology Development Centre of the General Hospital of the People’s Liberation Army).

Method of administration
Patients received orally 2.5 mg bisoprolol (purchased from Beijing Sihuan Pharmaceutical) every morning at 8 am after enrolment. They were followed up once every two weeks, and if the blood pressure had not reduced to normal, then the dose of bisoprolol was increased to 5 mg/d. Renin, Ang II and Ald levels in plasma and echocardiographic parameters were noted before and after treatment. Patients did not take any other drugs.

Judgment of the antihypertensive efficacy
Markedly: DBP decreased by ≥ 10 mmHg and fell to normal, or decreased by > 20 mmHg. Effective: DBP decreased by < 10 mmHg but returned to normal, or decreased by 10–19 mmHg as compared to the decline of > 30 mmHg in the treatment of systolic hypertension. Invalid: less than the above two criteria.

Statistical analysis
All data were analysed statistically using SPSS 17.0 software. Measurement data were presented as mean ± standard deviation (x ± s) and t-test was used; p < 0.05 was considered as statistically significant.

RESULTS
Antihypertensive efficacy
After two weeks of treatment, 27 cases did not meet the standard blood pressure, and the dose of bisoprolol was increased. Table 1 shows blood pressure control and efficiency after treatment for 2, 4, 8, 12 and 24 weeks.
Renin-angiotensin-aldosterone system and echocardiographic parameters

After 24 weeks, Ren, Ang II and Ald levels in plasma decreased, IVS and LVPW hypertrophy dropped, and LVMI also fell \( (p < 0.05) \) (Table 2).

Serum lipids

There was no significant difference between serum lipid parameters before and after 24 weeks of bisoprolol treatment \( (p > 0.05) \) (Table 3).

DISCUSSION

Hypertension can cause LVH (8). Left ventricular hypertrophy is an independent risk factor for cardiovascular disease (9). Cardiac hypertrophy and fibrosis is an integral part of left ventricular remodelling, and left ventricular remodelling is the pathological basis of congestive heart failure in patients with hypertension and systolic and diastolic dysfunction (10). The reversal and regression of LVH has become an important target for the treatment of hypertension. Studies have shown that ventricular remodelling and circulation are closely related to RAAS in tissue, and myocardial remodeling could be inhibited as RAAS was controlled (11). β-blockers can slow down the heart rate and inhibit myocardial contractility, thereby reducing blood pressure. They have been listed as essential drugs for the treatment of hypertension by the World Health Organization and the International Society of Hypertension. Bisoprolol is a type of selective β-blocker, a highly selective β1 receptor, with no intrinsic sympathomimetic activity. Oral use can improve the use of bioavailability and half-life, but there is no effect on the metabolism of lipids, renal function or blood glucose. Bisoprolol also has been reported to decrease the concentrations of Ren, Ang and Ald in plasma and improve the diastolic function of the left ventricle (12).

Some of the findings have important clinical implications considering that it is often suggested that Asians have a higher sensitivity to β-blockers compared to other populations, thereby requiring smaller doses (13, 14). In this study, a dose of oral bisoprolol (2.5–5 mg) once daily was given to 80 patients newly diagnosed with hypertension and LVH. The drug was easy to take; there was better compliance (not only was the antihypertensive effect better, but there were no obvious adverse reactions); it reduced Ren, Ang II and Ald levels in plasma and reversed LVH, as consistent with the literature (15). This study showed that a small dose of bisoprolol could lower blood pressure, inhibit the RAAS, suppress and

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>Markedly (n (%)</th>
<th>Effective (n (%))</th>
<th>Total efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>151.6 ± 13.2</td>
<td>97.4 ± 11.3</td>
<td></td>
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<tr>
<td>2 weeks</td>
<td>138.5 ± 11.2*</td>
<td>87.5 ± 10.0*</td>
<td>4 (10.3)</td>
<td>8 (20.5)</td>
<td>30.8</td>
</tr>
<tr>
<td>4 weeks</td>
<td>134.1 ± 13.1*</td>
<td>84.1 ± 9.0*</td>
<td>9 (24.7)</td>
<td>14 (35.7)</td>
<td>59.0</td>
</tr>
<tr>
<td>After</td>
<td>130.7 ± 9.6*</td>
<td>83.2 ± 10.5*</td>
<td>11 (28.2)</td>
<td>17 (43.6)</td>
<td>71.8</td>
</tr>
<tr>
<td>8 weeks</td>
<td>125.8 ± 10.3*</td>
<td>81.3 ± 7.7*</td>
<td>15 (38.5)</td>
<td>19 (48.7)</td>
<td>87.2</td>
</tr>
<tr>
<td>12 weeks</td>
<td>122.4 ± 12.5*</td>
<td>85.4 ± 10.1*</td>
<td>16 (41.0)</td>
<td>19 (48.7)</td>
<td>89.7</td>
</tr>
<tr>
<td>24 weeks</td>
<td>122.4 ± 12.5*</td>
<td>85.4 ± 10.1*</td>
<td>16 (41.0)</td>
<td>19 (48.7)</td>
<td>89.7</td>
</tr>
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</table>
| *Compared with readings before treatment, \( p < 0.05 \).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Plasma renin (μg/L)</th>
<th>Ang II (ng/L)</th>
<th>Ald (ng/L)</th>
<th>LVMI (g/m²)</th>
<th>IVS (mm)</th>
<th>LVPW (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>0.55 ± 0.21</td>
<td>55.9 ± 22.6</td>
<td>150.4 ± 37.7</td>
<td>144.0 ± 13.6</td>
<td>13.4 ± 1.8</td>
<td>12.8 ± 1.5</td>
</tr>
<tr>
<td>After</td>
<td>0.41 ± 0.19*</td>
<td>47.3 ± 23.6*</td>
<td>130.2 ± 29.8*</td>
<td>129.8 ± 16.1**</td>
<td>12.1 ± 1.3*</td>
<td>12.2 ± 1.3**</td>
</tr>
</tbody>
</table>
| Readings before and after treatment compared: * \( p < 0.01 \) and ** \( p < 0.05 \).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cholesterol (mmol/L)</th>
<th>LDL-C* (mmol/L)</th>
<th>HDL-C* (mmol/L)</th>
<th>Triglycerides (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>4.83 ± 0.75</td>
<td>2.96 ± 0.54</td>
<td>1.71 ± 0.39</td>
<td>1.77 ± 0.68</td>
</tr>
<tr>
<td>After</td>
<td>4.75 ± 0.69</td>
<td>2.91 ± 0.60</td>
<td>1.68 ± 0.42</td>
<td>1.82 ± 0.73</td>
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| *LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.
reverse ventricular remodelling, and improve the long-term prognosis in patients with hypertension.

REFERENCES