TO EVALUATE THE FEASIBILITY OF TREATING PREHYPERTENSION WITH AN ANGIOTENSIN RECEPTOR BLOCKER Candesartan Cilexetil

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ABSTRACT
Prehypertension is considered a precursor of stage 1 hypertension and a predictor of excessive cardiovascular risk. The trial of preventing hypertension (TROPHY) was an investigator-initiated study to examine whether early treatment of prehypertension, defined for this study as systolic blood pressure of 130 to 139 mmHg and diastolic blood pressure of 89 mmHg or lower and systolic pressure of 139 mmHg or lower, might prevent or delay the development of subsequent incident hypertension. The primary objective of the present study was to determine whether in patients with prehypertension six months of treatment with an angiotensin II, type 1 receptor antagonist (at a dose of 8mg once a day) reduces the incidence of hypertension in borderline patients.

Keywords: Prehypertension, candesartan Cilexetil, systolic blood pressure, diastolic blood pressure.

INTRODUCTION
The name of the range of blood pressure between what is clearly normal and what is definitely hypertensive changed from transient hypertension in the 1940s (Levy et al., 1944) to borderline hypertension in the 1970s (Julius and Schork, 1971) high-normal blood pressure in the 1990s (Anonymous, 1997) and most recently prehypertension in 2003 (Chobanian et al., 2003). Regardless of terminology, this condition is a precursor of hypertension (Leits et al., 1991) and is associated with excess morbidity and deaths from cardiovascular cause (Levy et al., 1945). Furthermore; an association of prehypertension with other cardiovascular risk factors has been established (Julius et al., 1990). We justified our study of pharmacological intervention with the use of an angiotensin-receptor blocker in prehypertension is based on following three grounds. One, in prehypertension, blood pressure remains a strong predictor of cardiovascular events after a statistical adjustment for other risk factors (Vasan et al., 2001) suggesting that lowering blood pressure might be beneficial. Hypertension is a self-accelerating condition. The transition from prehypertension to established hypertension reflects in part ongoing changes such as arterial hypertrophy (Folkow, 1982) and endothelial dysfunction (Panza et al., 1993).

Increased vasoconstriction and diminished vasodilatation, consistent with these structural and functional findings have been described in prehypertension (Eagan et al., 1987). Two, Growth factors mediated by stimulation of the sympathetic nervous system (Hart et al., 1980)
and excess activity of the renin-angiotensin system (Dzan, 2005) tend to promote vascular hypertrophy by direct as well as hemodynamic effects. Third, present guidelines recommend that prehypertension be managed with changes in the participant’s lifestyle, weight loss (Anonymous, 1997b), salt restriction, exercise, and dietary modifications have been shown to reduce blood pressure in clinics specializing in lifestyle modifications (Apple et al., 1997). Despite intensive community efforts to promote healthful lifestyles, however, the prevalence of prehypertension in the United States is increasing (Qureshi et al., 2000).

**SUBJECTS AND METHODS**

This study was conducted in the department of pharmacology and therapeutics, Basic Medical Sciences Institute (BMSI), in collaboration with the department of medicine, Jinnah Post-graduate Medical Centre, Karachi, from January 2007 to June 2007. This six months, randomized study involved eighty untreated participants between 30 to 60 years of age of either sex with blood pressure on study entry in high-normal range i.e., systolic blood pressure of 130 to 139 mmHg and diastolic blood pressure of 85 to 89 mmHg, according to the classification developed by Joint National Committee on prevention, Detection, Evaluation, and Treatment of high blood pressure (JNC-VI). All participants were randomized and enrolled in study after baseline investigations and informed written consent. The safety and tolerability were assessed by spontaneous reports of adverse events as observed and reported by the study participants and has been shown in table IC.

**Study Design**

The study period was consisted of 24 weeks with weekly follow-up visits of participants; but the observations of the parameters were recorded on day 0, day45 and day 90 of the study period. The selected participants were divided into two groups. DR1 (Candesartan) and DR2 (Placebo). The DR1 group received Tab. Candesartan 8mg once a day for 90 days, while DR2 group received Placebo once a day for 90 days. Following parameters were observed in the present study.

- Systolic blood pressure
- Diastolic blood pressure
- Safety profile

**STATISTICAL ANALYSIS**

All values have been expressed in standard error of mean (± SEM). The observations of the parameters were recorded in a tabulated form and paired students “t” test was used to analyze the data and observe the statistical significance of the results.

**RESULTS**

The results have been expressed as mean ± SEM (standard error of mean). Forty participants were treated with DR1 and DR2 from day 0 to day 90th of study duration respectively. In DR1 group the mean systolic blood pressure was decreased from 137.37 mmHg on day to 132.27 mmHg on day 45 and 126 mmHg on day 90th. This reduction was found statistically highly significant (P<0.001). The average percentage reduction in systolic B.P was 8.27 % from day 0 to day 90th of the treatment as shown in Table 1A and Fig. 1A. In DR2 group 40 study participants were treated form day 0 till day 90th of study duration. The mean systolic blood pressure was increased from 129 mmHg on day 0 to 132.7 mmHg on day 45th and 136.27 mmHg on day 90th of the treatment. This increase was also observed statistically significant. The average percentage increase in systolic blood pressure was observed 5.63% from day 0 to day 90th of treatment as depicted in Table 1A and Fig. 1A.

In DR1 group, the mean diastolic blood pressure on day 0 was 86.32 mmHg which reduce to 77.5 mmHg on day 45 and 76 mmHg on day 90th. This decrease in diastolic blood pressure was found statistically highly significant with a p- value (P<0.001), while in case of DR2 group the mean diastolic blood pressure was increased from 75.4 mmHg on
Jamali et al.

Changes in mean systolic B.P from Day 0 – Day 90, of the treatment with DR1, DR2 group

<table>
<thead>
<tr>
<th>Groups</th>
<th>At day 0 mmHg</th>
<th>At day 45 mmHg</th>
<th>At day 90 mmHg</th>
<th>P – value</th>
<th>%change day 0–day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Day 0-45</td>
<td>Day 45-90</td>
</tr>
<tr>
<td>DR1</td>
<td>137.37 ± 0.07 (40)</td>
<td>132.27 ± 0.3 (38)</td>
<td>126.08 ± 0.6 (38)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DR2</td>
<td>129 ± 0.41 (40)</td>
<td>132.7 ± 0.31 (36)</td>
<td>136.27 ± 0.2 (36)</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

Key: DR1 (Candesartan), DR 2 (Placebo), Values are in (mean ± SEM), All observations are in mmHg, ↓shows decrease in percentage, ↑ shows increase percentage.

The safety profile and drugs related undesired effects have been assessed by spontaneous reports of adverse events as observed and reported by the patients and has been shown in Table 1C.

**Fig. 1A. Changes in mean systolic B.P from day 0 – day 90 of treatment with DR1, DR2 group.**
Table 1-B
Changes in mean diastolic B.P from day 0 – day 90 of the treatment with DR1 & DR2 group

<table>
<thead>
<tr>
<th>Groups</th>
<th>At day 0 mmHg</th>
<th>At day 45 mmHg</th>
<th>At day 90 mmHg</th>
<th>P – value</th>
<th>%change day 0–day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR1</td>
<td>86.32 ± 0.2 (40)</td>
<td>77.5 ± 0.37 (38)</td>
<td>76 ± 0.33 (38)</td>
<td>&lt;0.001</td>
<td>&lt;0.001 &lt;0.001       ↓ 11.97%</td>
</tr>
<tr>
<td>DR2</td>
<td>75.4 ± 0.58 (40)</td>
<td>79.85 ± 0.19 (36)</td>
<td>84.5 ± 0.24 (36)</td>
<td>&lt;0.001</td>
<td>&lt;0.001 &lt;0.001       ↑ %12%</td>
</tr>
</tbody>
</table>

Key: DR1 (Candesartan), DR 2 (Placebo), Values are in (mean ± SEM), All observations are in mmHg. ↓ shows decrease in p, ↑ shows increase percentage.

Fig. 1B. Changes in mean diastolic B.P from day 0 – day 90 of the treatment with DR1 & DR2 group.

also be correlated with the findings of the Trial of Hypertension preventions.

Table 1-C
Observed and reported side effects with DR1 & DR2 group

<table>
<thead>
<tr>
<th>Headache</th>
<th>DR1</th>
<th>DR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>02</td>
<td>01</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>03</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>01</td>
<td>01</td>
</tr>
<tr>
<td>Dizziness</td>
<td>02</td>
<td>01</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>01</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>01</td>
<td>01</td>
</tr>
<tr>
<td>Edema</td>
<td>01</td>
<td>0</td>
</tr>
<tr>
<td>Nausea / Vomiting</td>
<td>02</td>
<td>01</td>
</tr>
<tr>
<td>Total Patients</td>
<td>13</td>
<td>05</td>
</tr>
</tbody>
</table>

CONCLUSION

Treatment of prehypertension with Candesartan Cilexetil may decreases incident hypertension. Additional studies will be needed to ascertain whether this or other strategies involving early pharmacological treatment of prehypertension would positively affect clinical outcomes.

REFERENCES


