Evaluation Of Safety of Azilsartan and Olmesartan In Patients Of Hypertension: Randomized Controlled Trial.

1Dr Deeksha Sharma, 2 Dr Dinesh Kansal , 3Dr Dhiraj Kapoor , 4 Dr Atal Sood

1MD Pharmacology, Dr RPGMC Kangra at Tanda, HP.
2Retired Professor, Department of Pharmacology, 3Professor & HOD. Department of Medicine, 4Professor, Department of Pharmacology.

Corresponding author:
Dr Deeksha Sharma
MD Pharmacology, Dr RPGMC Kangra at Tanda, HP

ABSTRACT: Background: Renin-angiotensin aldosterone system (RAAS) inhibitor either angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker (ARB) plus diuretic is a widely used for treatment of hypertension. Objective: To evaluate safety of azilsartan and olmesartan in patients of hypertension. Material and methods: A randomized, prospective, open label, comparative study was carried out in Pharmacology and Medicine department at Dr. R.P.G.M.C. Kangra at Tanda, HP. The study stretched over one year and haemoglobin (Hb), renal function test (RFT), liver function test (LFT), serum electrolytes were monitored at first, third and sixth month. Out of 69 patients, 35 patients in group A were prescribed tablet azilsartan 40 mg/day and 34 patients in group B were prescribed tablet olmesartan 20 mg/day along with chlorthalidone 12.5 mg/day in both the groups. Statistical analysis: Data was presented as mean ± SD. Student’s t-test was used for comparing continuous variables between the two groups. P value < 0.05 was considered significant. Results: Both the groups had normal range of haemoglobin, renal function test, liver function test and serum electrolyte over 6 months of period. There was no hepatotoxicity, nephrotoxicity, electrolyte imbalance and haematological toxicity observed in patients. Conclusion: Azilsartan and olmesartan were safe in patients of hypertension. Keywords: Azilsartan, Olmesartan, Hypertension, Safety.

INTRODUCTION
Hypertension is defined as high blood pressure or a long term medical condition in which the arterial blood pressure is continuously elevated.1 It is also explained as sustained diastolic BP more than 90 mm hg accompanied by the elevated systolic BP more than 140mmHg.2 More than two-thirds of hypertensive individuals are inadequately controlled on mono therapy. Combination therapy with a renin-angiotensin aldosterone system (RAAS) inhibitor (either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker (ARB) plus a diuretic is a widely used and effective approach that has become an established component of evidence-based hypertension treatment guidelines.3
Azilsartan medoxomil is a newly approved, effective, long-acting angiotensin II receptor blocker. ARBs are known for their relatively mild side-effect profile in comparison to other antihypertensive medications It is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and selective ARB with estimated bioavailability of 60% and half-life of12 hours.4 Diarrhea was the most common adverse effect associated with azilsartan medoxomil, occurring in up to 2% of patients receiving the 80-mg dose. Other adverse effects included nausea, asthenia, fatigue, muscle spasm, dizziness. Low hemoglobin, hematocrit, and red blood cell counts were observed in 0.2%, 0.4%, and 0.3% of patients respectively.5 Olmesartan medoxomil is an ARB with excellent efficacy and tolerability profile. It has long half-life which ensures effective BP control over the 24 h dosing interval. As a result, once daily dosing is required making the dosing regimen simple and improving patient compliance 6. The most common side effect is associated headache, which up to 7% of patients may experience, and 3% may have associated dizziness. The gastrointestinal system may also exhibit side effects, including abdominal pain, diarrhea. Very rare potential side effects include acute renal failure, alopecia, anaphylaxis, anxiety, chest pain, dyspepsia, eczema, erectile dysfunction, hyperbilirubinemia, hyperkalemia, hypotension, insomnia, and syncope.7 The aim of our study was to evaluate safety of azilsartan and olmesartan among patients of hypertension.
MATERIAL AND METHODS
The study was a randomized, prospective, open label, comparative interventional study and conducted in the Department of Medicine and Pharmacology at Dr. R.P.G.M.C, Kangra at Tanda. The study was undertaken during the period April 2020 to October 2021.
- IEC approval vide letter no. - IEC/29/2020
- CTRI registration no. REF/2020/03/032497

INCLUSION CRITERIA: The study included adult patients of either gender of hypertension.

EXCLUSION CRITERIA:
- Patients not willing to give written informed consent.
- Congestive heart failure NYHA classes II-IV.
- Recent major cardiovascular events (<6 months prior to randomization).
- Pregnant females.
- Patients already on treatment with study drugs.
- Known hypersensitivity to drugs.

CONSORT DIAGRAM
After a written informed consent, the participants were assigned to either group A or B, based on computer generated random numbers through simple randomization technique. Group A participants received tablet azilsartan 40 mg/day along with chlorthalidone 12.5 mg/day and group B participants received tablet olmesartan 20 mg/day along with chlorthalidone 12.5 mg/day in the morning.
Following baseline blood biochemical parameters were repeated on follow-ups at the end of first, third and sixth month after initiating the treatment.

- Hemoglobin count (Hb)
- Renal function tests (Serum creatinine, blood urea creatinine (BUN)
- Serum electrolytes (Na+, K+)
- Liver function test (SGOT, SGPT)

**MEASUREMENTS OF OUTCOME**

All the adverse events that occurred in subjects during study period were considered.

**STATISTICAL ANALYSIS**

Statistical analysis was done using microsoft excel and online ‘social science statistics’ software. Student’s t-test was used for comparing continuous variables between the two groups. P value < 0.05 was considered significant.

**RESULTS**

<table>
<thead>
<tr>
<th>Hb</th>
<th>Group A (n=35)</th>
<th>Group B (n=34)</th>
<th>p-value# Intergroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12.99±1.22</td>
<td>11.23±1.80</td>
<td>0.924</td>
</tr>
<tr>
<td>1-Month</td>
<td>12.95±1.11</td>
<td>11.11±1.72</td>
<td>0.819</td>
</tr>
<tr>
<td>3-Months</td>
<td>12.94±1.19</td>
<td>10.98±1.51</td>
<td>0.853</td>
</tr>
<tr>
<td>6-Months</td>
<td>12.84±1.07</td>
<td>11.33±1.61</td>
<td>0.816</td>
</tr>
<tr>
<td>p-value* Intra group</td>
<td>Baseline vs. 1-month &lt;0.098</td>
<td>Baseline vs. 1-month &lt;0.300</td>
<td>Baseline vs. 1-month &lt;0.196</td>
</tr>
<tr>
<td></td>
<td>Baseline vs. 3-months &lt;0.083</td>
<td>Baseline vs. 3-months &lt;0.248</td>
<td>Baseline vs. 3-months &lt;0.196</td>
</tr>
<tr>
<td></td>
<td>Baseline vs. 6-months &lt;0.072</td>
<td>Baseline vs. 6-months &lt;0.196</td>
<td>Baseline vs. 6-months &lt;0.196</td>
</tr>
</tbody>
</table>

Data expressed as mean ±SD

#Un paired student t-test (Intergroup comparison)

*Paired student t- test (Intra group comparison)
**RENAL FUNCTION TEST**

1) **CREATININE**

Table 2: Comparison of creatinine between two groups

<table>
<thead>
<tr>
<th>Creatinine</th>
<th>Group A (n=35)</th>
<th>Group B (n=34)</th>
<th>p-value# Intergroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.00±0.14</td>
<td>0.99±0.16</td>
<td>0.748</td>
</tr>
<tr>
<td>1-Months</td>
<td>0.85±0.10</td>
<td>0.83±0.13</td>
<td>0.263</td>
</tr>
<tr>
<td>3-Months</td>
<td>0.83±0.14</td>
<td>0.82±0.15</td>
<td>0.226</td>
</tr>
<tr>
<td>6-Months</td>
<td>0.82±0.14</td>
<td>0.82±0.16</td>
<td>0.264</td>
</tr>
</tbody>
</table>

*p-value*

Intra group

Baseline vs. 1-month <0.244
Baseline vs. 3-months <0.196
Baseline vs. 6-months <0.164

Baseline vs. 1-month <0.474
Baseline vs. 3-months <0.321
Baseline vs. 6-months <0.234

Data expressed as mean ±SD

# Un paired student t-test (Intergroup comparison)

*Paired student t-test (Intra group comparison)

---

2) **BLOOD UREA NITROGEN (BUN)**

Table 3: Comparison of BUN levels between two groups

<table>
<thead>
<tr>
<th>BUN</th>
<th>Group A (n=35)</th>
<th>Group B (n=34)</th>
<th>p-value# Intergroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24.07±5.28</td>
<td>24.45±6.24</td>
<td>0.421</td>
</tr>
<tr>
<td>1-Months</td>
<td>24.87±7.72</td>
<td>22.66±6.01</td>
<td>0.198</td>
</tr>
<tr>
<td>3-Months</td>
<td>23.90±7.35</td>
<td>20.93±5.17</td>
<td>0.061</td>
</tr>
<tr>
<td>6-Months</td>
<td>23.60±6.41</td>
<td>21.84±4.82</td>
<td>0.210</td>
</tr>
</tbody>
</table>

*p-value*

Intra group

Baseline vs. 1-month <0.356
Baseline vs. 3-months <0.256
Baseline vs. 6-months <0.123

Baseline vs. 1-month <0.133
Baseline vs. 3-months <0.109
Baseline vs. 6-months <0.059

Data expressed as mean ±SD

# Un paired student t-test (Intergroup comparison),

*Paired student t-test (Intra group comparison)
SERUM ELECTROLYTES (SODIUM)

Table 4: Comparison of sodium levels between two groups

<table>
<thead>
<tr>
<th>Na+</th>
<th>Group A (n=35)</th>
<th>Group B (n=34)</th>
<th>p-value# Intergroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>138.91±5.84</td>
<td>140.09±3.62</td>
<td>0.324</td>
</tr>
<tr>
<td>1-Month</td>
<td>138.33±5.79</td>
<td>139.09±3.08</td>
<td>0.563</td>
</tr>
<tr>
<td>3-Months</td>
<td>138.80±2.96</td>
<td>138.21±5.72</td>
<td>0.930</td>
</tr>
<tr>
<td>6-Months</td>
<td>138.88±3.13</td>
<td>138.88±3.13</td>
<td>0.913</td>
</tr>
</tbody>
</table>

*p-value* Baseline vs. 1-month <0.265
Baseline vs. 3-months <0.194
Baseline vs. 6-months <0.162
Baseline vs. 1-month <0.200
Baseline vs. 3-months <0.184
Baseline vs. 6-months <0.147

Data expressed as mean ±SD
# Un paired student t-test (Intergroup comparison)
*Paired student t-test (Intra group comparison)
**POTASSIUM**

Table 5: Comparison of potassium levels in two groups

<table>
<thead>
<tr>
<th>Time Line</th>
<th>Group A (n=35)</th>
<th>Group B (n=34)</th>
<th>p-value# Intergroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.13±0.49</td>
<td>4.04±0.38</td>
<td>0.409</td>
</tr>
<tr>
<td>1-Month</td>
<td>4.06±0.40</td>
<td>3.95±0.28</td>
<td>0.192</td>
</tr>
<tr>
<td>3-Months</td>
<td>4.04±0.47</td>
<td>3.98±0.41</td>
<td>0.613</td>
</tr>
<tr>
<td>6-Months</td>
<td>3.97±0.37</td>
<td>3.94±0.32</td>
<td>0.749</td>
</tr>
</tbody>
</table>

p-value* Intra group

Baseline vs. 1-month < 0.220
Baseline vs. 3-months < 0.165
Baseline vs. 6-months < 0.123

Data expressed as mean ±SD

# Un paired student t-test (Intergroup comparison)

*Paired student t-test (Intra group comparison)

---

**LIVER FUNCTION TEST**

1) Serum glutamate oxaloacetate transaminase (SGOT)

Table 6: Comparison of SGOT level between two groups

<table>
<thead>
<tr>
<th>Time Line</th>
<th>Group A (n=35)</th>
<th>Group B (n=34)</th>
<th>p-value# Intergroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>41.78±7.54</td>
<td>42.03±9.86</td>
<td>0.218</td>
</tr>
<tr>
<td>1-Month</td>
<td>36.28±7.67</td>
<td>40.20±7.89</td>
<td>0.145</td>
</tr>
<tr>
<td>3-Months</td>
<td>33.05±7.68</td>
<td>36.88±6.88</td>
<td>0.113</td>
</tr>
<tr>
<td>6-Months</td>
<td>34.97±9.09</td>
<td>34.06±6.57</td>
<td>0.641</td>
</tr>
</tbody>
</table>

p-value* Intra group

Baseline vs. 1-month < 0.098
Baseline vs. 3-months < 0.071
Baseline vs. 6-months < 0.061

Data expressed as mean ±SD

# Un paired student t-test (Intergroup comparison)

*Paired student t-test (Intra group comparison)
2) Serum glutamate pyruvate transaminase (SGPT)

Table 7: Comparison of SGPT level between two groups

<table>
<thead>
<tr>
<th>SGPT</th>
<th>Group A (n=35)</th>
<th>Group B (n=34)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>33.32±6.95</td>
<td>32.72±8.68</td>
<td>0.758</td>
</tr>
<tr>
<td>1-Month</td>
<td>30.72±6.49</td>
<td>33.24±6.30</td>
<td>0.114</td>
</tr>
<tr>
<td>3-Months</td>
<td>33.53±7.87</td>
<td>31.06±6.65</td>
<td>0.172</td>
</tr>
<tr>
<td>6-Months</td>
<td>29.91±8.83</td>
<td>27.78±6.77</td>
<td>0.275</td>
</tr>
</tbody>
</table>

p value*:
- Baseline vs. 1-month < 0.312
- Baseline vs. 3-months < 0.236
- Baseline vs. 6-months < 0.123

Data expressed as mean ±SD
# Un paired student t-test (Intergroup comparison)
*Paired student t-test (Intergroup comparison)

As shown in Table 1, the patients in group A had comparable Hb to group B at baseline (p=0.924), at 1-month (p=0.819), at 3-months (p=0.853), and at 6-months (p=0.816).

In table 2, the patients in group A had comparable creatinine to group B at baseline (p=0.748), at 1-month (p=0.263), at 3-months (p=0.226), and 6-months (p=0.264). In table 3, in group A had comparable urea to group B at baseline (p=0.421), at 1-month (p=0.198), at 3-months (p=0.061), and at 6-months (p=0.210).
In table 4, group A had comparable sodium to group B at baseline (p=0.324), at 1-month (p=0.563), at 3-months (p=0.930), and at 6-months (p=0.913) and the patients in group A had comparable potassium to group B at baseline (p=0.409), at 1-month (p=0.192), at 3-months (p=0.613), and at 6-months (p=0.749) in table 5.

In table 6, the patients in group A had comparable SGOT levels to group B at baseline (p=0.218), at 1-month (p=0.145), at 3-months (p=0.641) and at 6-months (p=0.758), at 1-month (p=0.114), at 3-months (p=0.172), and at 6-months (p=0.275) in table 7.

DISCUSSION
Our study results showed no adverse events. Hemogram (Hb count), liver function test (SGOT, SGPT), renal function test (blood urea nitrogen, serum creatinine), electrolytes (serum sodium, serum potassium) remained within normal range over 6 months (24 weeks) in both the groups. This observation suggests that both drugs were safe in the given population.

LIMITATIONS
This study being post graduate thesis, the follow-up could not be extended beyond 6 months. Follow-up for longer duration would have added more evidence about safety of our drugs.

CONCLUSION
Both the drugs didn’t have any haematological toxicity, renal toxicity, liver toxicity and electrolyte imbalance. Azilsartan and olmesartan were safe in patients of hypertension.

FINANCIAL DISCLOSURE
No unnecessary financial burden was put on the patient for the treatment and investigations at any point of time throughout the study period. I did not get any financial benefit from any pharmaceutical company or any other source for this study.

CONFLICT OF INTEREST
No conflict of interest pertaining to any part of the study.

REFERENCES