Start of therapy with the angiotensin II antagonist losartan after immediate switch from pretreatment with an ACE inhibitor

Juergen Scholze & Manfred Stapff
1Humboldt-University, Charite, Berlin, and 2MSD Sharp & Dohme GmbH, Haar b. Muenchen, Germany

Aims To evaluate initial blood pressure effects of the angiotensin II antagonist losartan (L) immediately after switching from an ACE inhibitor (captopril, C).

Methods Two-phase multicentre randomized study in 177 outpatients with mild to moderate essential hypertension. For 6 weeks all patients received 25 mg C twice daily. Then they were randomized double-blind to switch for another 6 weeks to 50 mg L once daily (n = 110) or to maintain C (n = 55). On the first day of the switch they underwent ambulatory blood pressure measurement (ABPM).

Results Within 12 h of first dose, 31% of patients who switched to L had two consecutive systolic BP readings of 30 mmHg below their individual baseline value compared with 24% of patients who stayed on C. In 3% of patients with L and in 6% of the C patients systolic BP readings less than 100 mmHg were recorded within 12 h of first dose. The differences were not statistically significant. There were no clinical symptoms attributable to initial hypotension. During the 6 weeks double-blind therapy, 9% of L patients experienced at least one adverse event, compared with 16% of patients with C.

Conclusions In this study the angiotensin II antagonist losartan was effective and generally well tolerated when administered immediately after pretreatment with an ACE inhibitor.

Keywords: angiotensin antagonism, captopril, losartan, switch, ambulatory BP monitoring

Introduction
Angiotensin II AT1-subtype receptor antagonists are a new class of antihypertensive agents of which losartan (L) is the first and most extensively studied compound [1, 2].

ACE inhibitors, in addition to reducing the production of angiotensin II, may lead to accumulation of vasodilatory kinins by inhibiting the enzyme kininase II and might therefore have an additional hypotensive effect.

After an initial dose of ACE inhibitors or angiotensin II antagonists symptomatic hypotensive episodes have been observed when the RAAS had been stimulated by sodium/water deficiency [3, 4], diuretic pretreatment or by diseases such as heart failure [5]. This trial was designed to evaluate the initial blood pressure response when hypertensive patients on captopril 25 mg twice daily are switched directly to 50 mg losartan.

Methods

Patients

This multicentre study was performed in 177 Caucasian outpatients with mild to moderate essential hypertension. Written informed consent according to the Declaration of Helsinki was obtained from every patient before inclusion.

Patients had to have at least two documented sitting blood pressure measurements above 160 mm Hg systolic and 95 mmHg diastolic (diastolic maximum: 115 mmHg) during the screening period. Renal function had to be normal (blood urea <12.5 mmol l⁻¹ and serum creatinine <150 μmol l⁻¹). Patients with heart failure or any other clinically significant cardiopulmonary, hepatic, metabolic or neurological disorders, with drug- or alcohol abuse or with any contraindication to AII antagonists or ACE inhibitors were excluded. The most common concomitant diagnoses were lipid disorders (41%), diabetes mellitus (22%) and hyperuricaemia (16%).

Study design

This was a controlled, randomized, double-blind parallel multicentre study. Patient did not receive any other antihypertensive or vasodilatory medication except the study drug. After a 6 weeks single-blind phase with captopril 25 mg twice daily patients were randomly assigned double-blind to switch to losartan 50 mg once daily or to keep their medication with captopril, each for further 6 weeks. As not unusual in comparative studies with new drugs an imbalanced design with 2:1 randomization was chosen to gather safety information with the new compound.

Ethics

The study protocol including the informed consent form had been reviewed and approved locally by the ethical
review boards responsible for each single centre. It was conducted and monitored according to the European Guidelines for Good Clinical Practice (GCP).

**Blood pressure measurement techniques**

An automatic 24 h oscillometric monitor (Spacelabs) was used. The measurement intervals were 15 min during the day and 30 min at night (22.00 h–06.00 h). Patients underwent a first 24 h ambulatory blood pressure monitoring (ABPM) during the captopril phase and a second 24 h ABPM at the first day of the double-blind phase. This second 24 h ABPM measurement period began 12 h after the last dose of captopril, with the first double-blind dose, either losartan 50 mg (switch arm) or with continuation of the morning dose captopril 25 mg (maintained arm).

**Statistics**

The incidence of initial symptomatic hypotension following the first dose of an ACE-inhibitor in hypertensive patients is reported between 0.7 and 10% depending on definition and type of study [12]. The purpose of this trial was to document the incidence of asymptomatic hypotension as determined by 24 h blood pressure monitoring. The study was powered to detect overshooting reductions in systolic blood pressure with an incidence of at least 15% in the losartan group with 95% probability. Such episodes were defined as:

1. A fall >30 mmHg in systolic BP within 12 h of the first dose (confirmed by two consecutive ABPM readings) or
2. Two consecutive systolic BP readings <100 mmHg within the first 12 h.

Since the study was not designed for comparisons between groups, descriptive statistics are presented as an estimate and 95% confidence interval of the relative risk of asymptomatic hypotension.

**Results**

One hundred and seventy-seven patients were recruited into the baseline phase, of which 163 (63 female and 102 male) were randomized into the double-blind portion of the study. The treatment groups did not significantly differ regarding age, gender, secondary diagnoses and severity of hypertension. One hundred and five patients (95%) completed losartan treatment and 51 patients (93%) finished the trial on captopril. Due to missing or incomplete ABPM measurements 21 patients had to be excluded from the analysis of initial hypotension. These patients did not differ with respect to demographics or diagnoses from the entire sample. Thus data of 94 patients switching to losartan and EXP 3174 are reached after about 4.5 h; the half-life is approximately 6–9 h [6, 7]. On the basis of these pharmacokinetic data, an antihypertensive effect with a slow onset lasting over 24 h is expected and has been shown in several clinical studies [8–10]. Initial hypotensive episodes, particularly with clinical symptoms, are extremely rare [11].

**Ambulatory blood pressure measurement after switch of therapy**

ABPM measurement of the first day of the double-blind phase started 12 h after the last intake of captopril 25 mg, when patients were administered the first dose of double-blind therapy. A fall of systolic BP >30 mmHg (or <100 mmHg), was experienced in 31% (3%) of patients who switched to losartan compared with 24% (6%) of patients continuing with captopril (Table 1). The relative risk of such asymptomatic initial hypotensive episodes after switching from C to L compared with staying with C was 1.01 (95% confidence interval: 0.63 to 1.75).

Figure 1 compares the two 24 h ABPM profiles of the first day of double-blind therapy. While captopril showed a trend towards an earlier peak effect, there were no significant differences in the course of the curves. Especially there was no decrease in BP within the first 12 h exceeding the normal circadian rhythm.

**Tolerability and adverse events**

No clinical symptoms of hypotension were recorded during the starting day of the double-blind treatment period.

Within the open baseline phase of 6 weeks, when all 177 patients received 25 mg captopril twice daily, 25 (14%) patients reported at least one clinical adverse event (AE). During the 6 week double-blind phase at least one AE was reported by 9% in the losartan group and by 16% in the captopril group. The relative risk of experiencing any clinical adverse experience in the 6 weeks after switch from captopril to losartan, compared to staying on captopril for another 6 weeks, was 0.56 (95% confidence interval: 0.25 to 1.26). None of the AEs was serious.

Headache (in 3% of patients with losartan and 5% with captopril) was the adverse event most frequently reported.

**Discussion**

Starting therapy interfering with the renin angiotensin system (RAS), e.g. with ACE inhibitors or angiotensin II antagonists, can result in an initial overshooting blood pressure reduction [12]. Especially after pretreatment with diuretics or during conditions of salt or water deficiency the RAS is stimulated, and first doses of ACE inhibitors are the most specific blockers of the RAS [14, 15]. Thus the question whether angiotensin II receptor blockers can be used. The measurement intervals were 15 min during the day and 30 min at night (22.00 h–06.00 h). Patients underwent a first 24 h ambulatory blood pressure monitoring (ABPM) during the captopril phase and a second 24 h ABPM at the first day of the double-blind phase. This second 24 h ABPM measurement period began 12 h after the last dose of captopril, with the first double-blind dose, either losartan 50 mg (switch arm) or with continuation of the morning dose captopril 25 mg (maintained arm).
Table 1 Ambulatory blood pressure monitoring (ABPM) data before and after switch of therapy.

<table>
<thead>
<tr>
<th></th>
<th>Group switched to losartan (n = 94)</th>
<th>Group staying with captopril (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24 h mean (ABP, mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before switch</td>
<td>138.7/84.4</td>
<td>141.4/86.5</td>
</tr>
<tr>
<td>after switch</td>
<td>137.4/83.4</td>
<td>140.0/85.6</td>
</tr>
<tr>
<td><strong>12 h daytime mean (ABP, mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before switch</td>
<td>145.9/9.0/9.0</td>
<td>145.9/1.2</td>
</tr>
<tr>
<td>after switch</td>
<td>141.7/87.5</td>
<td>145.3/90.5</td>
</tr>
<tr>
<td><strong>Patients with systolic BP &lt; 100 mmHg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (3%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td><strong>Patients with systolic fall &gt; 30 mmHg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 (31%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td><strong>Percentage of patients with ‘hypotension’</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>(22%—41%)</td>
<td>(17—43%)</td>
</tr>
<tr>
<td><strong>Any adverse event during 6 weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>double-blind therapy</td>
<td>10 (9%)</td>
<td>9 (16%)**</td>
</tr>
</tbody>
</table>

* = Between group comparison: 1.06 (95% CI: 0.63, 1.75). ** = Between group comparison: NS.

The study was designed to look for the percentage of patients experiencing any symptomatic or asymptomatic fall of systolic blood pressure (defined as a decrease > 30 mmHg or to an absolute value < 100 mmHg).

Between the losartan and captopril control group there was no statistically or clinically relevant difference in the number of patients whose systolic blood pressure decreased significantly. No clinical adverse event was seen which could be attributed to a first dose reaction during switch from captopril to losartan.

As in other trials with losartan [9, 10, 16] clinical adverse events were infrequent, generally non-serious and of mild intensity. Despite lacking statistical significance it is noteworthy that switch from captopril to losartan reduced the incidence of experiencing an adverse event by 44% compared with maintaining therapy with the ACE inhibitor.

In summary, in this study the angiotensin II antagonist losartan was effective and generally well tolerated when administered immediately after pretreatment with an ACE inhibitor.
The study was supported by a grant of Merck & Co Inc, Whitehouse Station, PA, USA

References


(Revised 24 November 1997, accepted 4 March 1998)