

Clinical Experience With Angiotensin II Receptor Antagonists

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This series of studies was designed to assess in normal volunteers the relationships between various doses (5, 10, 20, 40, 80, and 120 mg) of the orally active angiotensin II antagonist losartan (DuP 753, MK-954) and their inhibitory effect on the pressure response to a given bolus of angiotensin I or II. It was found that the maximal inhibitory effect was reached with a dose of 80 mg. The minimal dose necessary for maximal efficacy would therefore be expected to be between 40 and 80 mg. The effect lasted for more than 24 h and was related almost

exclusively to the circulating levels of the active metabolite EXP3174. It remains to be demonstrated in hypertensive patients that the same dose relationship holds for the antihypertensive effect, but preliminary data already suggest that this is the case. *Am J Hypertens* 1992;5:243S-246S

KEY WORDS: Angiotensin II receptor antagonists, renin-angiotensin system, losartan, DuP 753, anti-hypertensive agents.

Interruption of the renin-angiotensin system (RAS) as a means of controlling hypertension has received a great deal of attention in recent years. The most useful therapeutic agents to evolve from these investigations are the angiotensin converting enzyme (ACE) inhibitors. Captopril¹ and enalapril,² which were initially introduced for treating severe or renin-dependent hypertension, have been shown to be effective in managing milder forms of essential hypertension in which there is no clear activation of the renin-angiotensin system. This suggests that the renin-angiotensin system plays a broader role in the pathophysiology of hypertension.³

While ACE inhibition is effective in controlling blood pressure, this does not occur without some side effects such as cough and angioedema. These side effects are believed to be related to the fact that ACE, which is a relatively nonspecific peptidyl dipeptidase, is involved

in the breakdown of bradykinin. Inhibition of ACE thus leads to potentiation of bradykinin actions, which may be responsible for the side effects.

Recently, specific, orally active, nonpeptide angiotensin II (ANG II) receptor antagonists have been developed.⁴ Losartan is the first of these agents to enter clinical trials. The potential advantages of this approach to blocking the renin-angiotensin system are that, by inhibiting the hormone from binding to its receptor, the system can be specifically turned off regardless of the source of ANG II. In addition, since ACE is not affected, there is no potentiation of bradykinin and, therefore, no cough or angioedema would be expected during therapy with losartan.

METHODS

The initial studies in human subjects assessed the tolerance and inhibitory effect of losartan (DuP 753) on the pressor action of exogenous ANG I or ANG II. In the first study, single oral doses of losartan (2.5, 5, 10, 20, and 40 mg) were studied *v* placebo.⁵ A dose-response relationship was established with regard to systolic blood pressure responses to increasing intravenous doses of ANG (I or II) in each subject. The test dose of

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ANG I selected was one that increased systolic blood pressure by about 30 mm Hg. This dose was then used to define the baseline systolic blood pressure response to ANG and became the challenge dose for that subject. The effect of losartan was established by bolus injections of the challenge dose of ANG given from 15 min to 27 h after ingestion of losartan (dissolved in 20 mL of tap water).

RESULTS

Losartan had no effect on resting blood pressure or heart rate and was well-tolerated in this study. Doses of 2.5 and 5 mg of losartan had no effect on systolic blood pressure response to ANG I when compared with placebo. Doses of 10, 20, and 40 mg of losartan produced a dose-related inhibition of the systolic blood pressure response to ANG I (Figure 1), which was accompanied by increases in plasma ANG II. Plasma aldosterone levels fell after the administration of losartan, but these changes were not different from placebo (Figure 2).

From Figure 1 it is evident that the duration of the ANG I-blocking effect of losartan is prolonged, up to 24 h or more at the 40 mg dose. Figure 3 compares the time course of the mean plasma levels of losartan with the levels of immunoreactive ANG II and with the inhibition of the systolic blood pressure response to ANG I after single oral doses of 20 and 40 mg losartan. It is clear that the effects on systolic blood pressure and immunoreactive ANG II persist long after plasma levels of losartan have disappeared. The prolonged effects of the drug are due to the presence of the active metabolite E-3174, which has a half-life of approximately 6.5 h.

The second study of losartan in human subjects was a multiple-dose tolerance study, which also assessed the inhibitory effects of repeated dosing with losartan on the response of systolic blood pressure to ANG II.⁶ The doses of losartan studied were 5, 10, 20, or 40 mg, given orally once a day for 8 days. These doses were compared

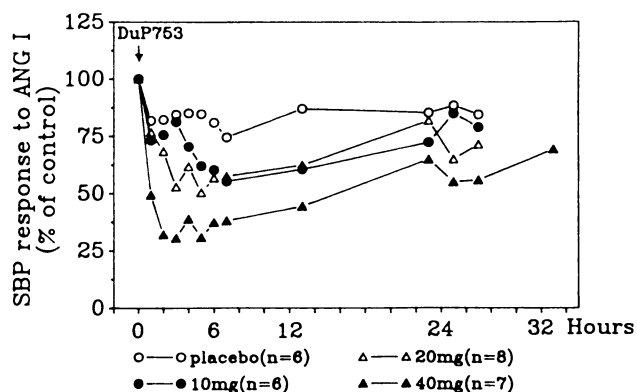


FIGURE 1. Plots of effects of single doses of oral DuP 753 (10, 20, or 40 mg) or placebo on systolic blood pressure (SBP) response (mean) to test doses of angiotensin I (ANG I) in healthy volunteers.

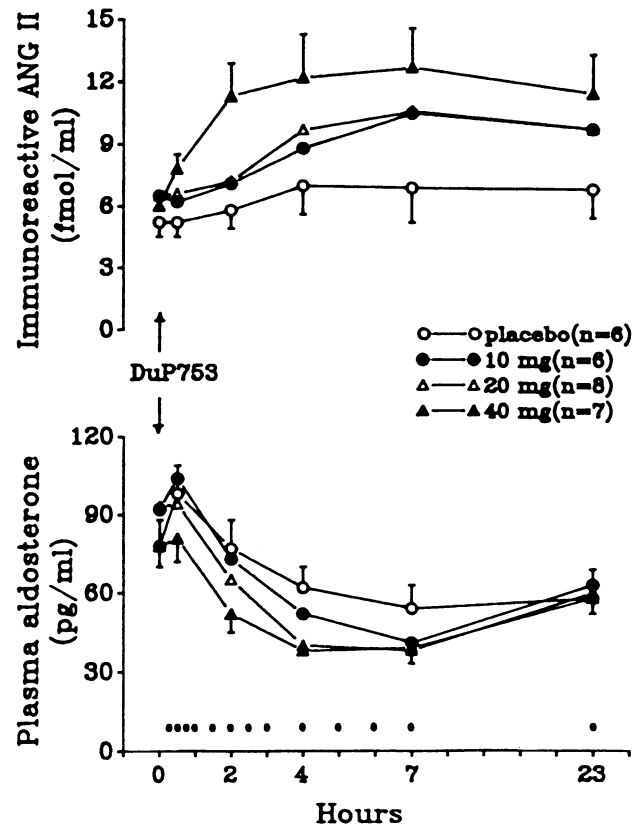


FIGURE 2. Effects of single doses of oral DuP 753 (10, 20, or 40 mg) or placebo on plasma aldosterone (lower panel) and immunoreactive angiotensin II (ANG II) (upper panel). Bullets on abscissa, ANG I test-dose injections. Values are given as mean \pm SEM.

with placebo given for 8 days. This study was carried out in a similar fashion to the single-dose study, in that dose-response relationships were established with regard to the systolic blood pressure response to exogenous ANG II. The challenge dose was again targeted to cause an approximately 30 mm Hg increase in systolic blood pressure. The ANG II challenge was carried out on days 2, 4, and 8 before and 6 and 12 h following ingestion of losartan or placebo. Additional challenges were performed 24 h before administration of the drug on day 1, and at 24, 30, and 36 h after the last dose on day 8.

Losartan was well-tolerated in this study, with no clinically significant side effects observed after multiple dosing. As in the first study, losartan had no effect on resting blood pressure or heart rate.

Losartan (10 to 40 mg) caused a dose-dependent decrease in the systolic blood pressure response to ANG II throughout the treatment period, when compared with placebo. The degree of blockade achieved with the 20 and 40 mg doses was similar 6 h after drug intake on

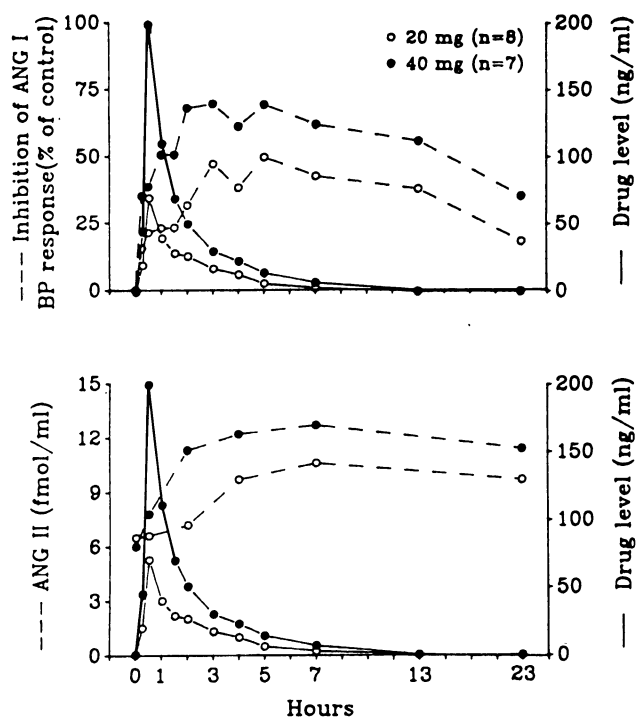


FIGURE 3. Comparisons of DuP 753 plasma levels (mean) with inhibition of systolic blood pressure (BP) response to test doses of angiotensin I (ANG I) (**upper panel**) and immunoreactive ANG II (**lower panel**) after single oral doses of DuP 753 (20 and 40 mg).

days 1, 4, and 8 ($P < .01$) compared with placebo. On days 4 and 8, subjects receiving 40 mg losartan showed a clear trend toward a reduced response to ANG II immediately before the morning dose of the drug (Figure 4). At peak effect, the 40 mg doses of losartan caused an approximately 70% reduction in the systolic blood pressure response to ANG II.

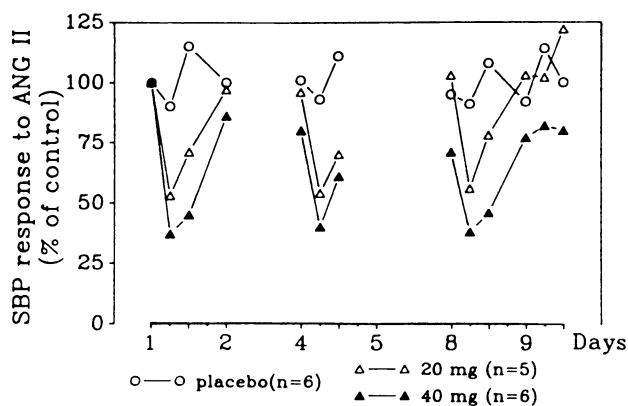


FIGURE 4. Plots of effects of 8 consecutive days of treatment with two oral doses of either DuP 753 (20 or 40 mg) or placebo on systolic blood pressure (SBP) response (mean) to test doses of angiotensin II (ANG II) in healthy volunteers.

Plasma renin activity and ANG II levels also responded with a dose-dependent compensatory rise which was more pronounced on day 8 than on day 1 of drug administration (Figure 5). The long duration of the blocking effect of losartan is reflected in the plasma renin activity and ANG II levels on day 8; these levels were clearly increased prior to the administration of the 20 and 40 mg dose. This prolonged duration of action is undoubtedly due to the presence of the active metabolite of losartan (E-3174).

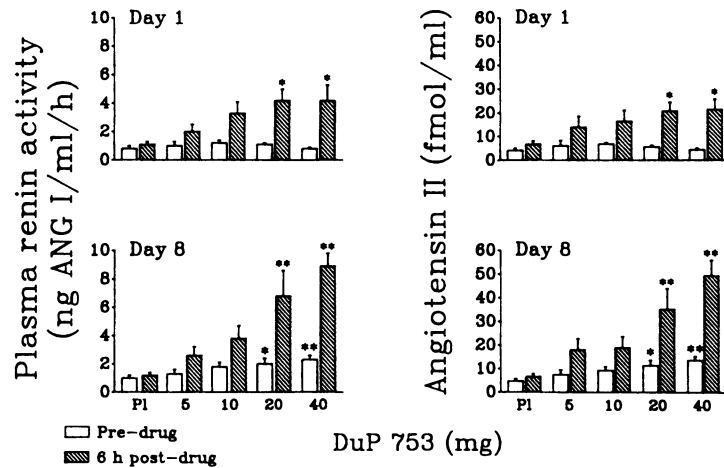
Subsequently, the effects of 40, 80, and 120 mg oral doses of losartan on systolic blood pressure responses to ANG II were studied in the same fashion. The 80 mg dose produced a maximal blockade of the systolic blood pressure response to ANG II ($> 80\%$).⁶ In this study, Munafo and coworkers investigated the relationships between plasma concentrations of losartan; its active metabolite, E-3174; and ANG II blockade in six healthy subjects who received 40, 80, or 120 mg of losartan or placebo at 1 week intervals in a cross-over protocol. E-3174 reached higher plasma concentrations and was eliminated more slowly than losartan; E-3174 plasma levels paralleled the profile of ANG II blockade more closely than did plasma levels of losartan. The inhibition of the blood pressure response was dose-dependent. The concentration-response curve suggested that E-3174 levels higher than about 200 ng/mL do not further enhance the effect. There was no gain in either the degree or the duration of inhibition from increasing the oral dose of losartan beyond 80 mg.

The reactive increase in plasma renin activity and circulating ANG II in these normotensive subjects was highly variable and could not be used to predict the inhibition in individual subjects. The researchers concluded that the effect of losartan is most likely attributable to the long-acting metabolite E-3174.

DISCUSSION

The results of these studies led to the expectation that the effective antihypertensive dose of losartan would be between 40 and 80 mg and would have a duration of effect that would support a once-daily dose regimen. Nelson and coworkers⁷ have reported the antihypertensive effects of losartan (50, 100, or 150 mg taken orally once daily) compared with placebo and 10 mg enalapril taken orally once daily in 98 mildly to moderately hypertensive patients. After 5 days of dosing, a significant decrease in both systolic and diastolic blood pressure was seen when compared with placebo. There was no difference in the magnitude of response between the three doses of losartan or the 10 mg dose of enalapril. It would appear that the losartan doses studied are at the high end of the dose-response curve, since 100 and 150 mg doses had no additional effect on blood pressure.

FIGURE 5. Effects of four different daily oral doses of DuP 753 (5, 10, 20, or 40 mg) or placebo ($n = 6$ for each dose except dose of 20 mg, where $n = 5$) on plasma renin activity and immunoreactive angiotensin II (ANG II), measured before and 6 h after drug intake on days 1 and 8. Values are given as mean \pm standard error of the mean. * $P < .05$. ** $P < .01$ v placebo.



Further studies are in progress to define the dose-response relationships of losartan with regard to blood-pressure lowering.

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