Oral Administration of DuP 753, a Specific Angiotensin II Receptor Antagonist, to Normal Male Volunteers

Inhibition of Pressor Response to Exogenous Angiotensin I and II

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**Background.** The purpose of the present study was to assess the inhibitory effect of DuP 753, an orally active angiotensin II receptor antagonist, on the pressor action of exogenous angiotensin I and II in healthy male volunteers.

**Methods and Results.** In the first study (single-dose study), eight volunteers were included in a 2-day protocol repeated four times at 1-week intervals. In each phase, a different dose of drug (2.5, 5, 10, 20, or 40 mg) or placebo was given. The peak systolic blood pressure response to a test-dose of angiotensin I was determined serially before and after oral administration of DuP 753 by continuously monitoring finger blood pressure using a photoplethysmographic method. DuP 753 reduced the systolic blood pressure response to angiotensin I in a dose-dependent fashion. Three, 6, and 13 hours after the 40-mg dose, blood pressure response decreased to 31±5%, 37±6%, and 45±3% of the control values (mean±SEM, n=7), respectively. In the second study, 29 volunteers were treated for 8 days with either a placebo or DuP 753 (5, 10, 20, or 40 mg p.o. q.d.) and challenged on the first, fourth, and eighth days with bolus injections of angiotensin II. Again, the inhibitory effect on the systolic blood pressure response to angiotensin II was clearly dose dependent. Six hours after 40 mg DuP 753, the systolic blood pressure response to the test-dose of angiotensin II was reduced to 37±7%, 40±4%, and 38±6% of baseline values (mean±SEM, n=6) on days 1, 4, and 8, respectively. With this latter dose, there was still a blocking effect detectable 24 hours after the drug. Similar to angiotensin converting enzyme and renin inhibitors, DuP 753 induced a dose-dependent increase in plasma renin that was more pronounced on the eighth than on the first day of drug administration. In these normal volunteers, no consistent clinically significant side effects were observed. There was no evidence for an agonist effect.

**Conclusions.** DuP 753 appears to be a well-tolerated, orally active, potent, and long-lasting antagonist of angiotensin II in men. (Circulation 1991;83:1333–1342)
Subsequently, drugs were developed that were intended to reduce circulating Ang II. Today, the angiotensin converting enzyme (ACE) inhibitors are widely used to treat hypertension and congestive heart failure. Many compounds are available that are both very effective and usually well tolerated. However, some class-specific side effects as cough, a quite frequent problem, and angioneurotic edema, a more serious but rare disorder, are encountered. It appears not unreasonable to relate these side effects to the lack of specificity of ACE inhibitors, which not only block the conversion of Ang I to Ang II but also reduce the degradation of bradykinin and substance P, two peptides capable of triggering cough. For this reason, the more specific enzyme renin has recently become the target for inhibition, but such compounds are still in the early development stage.

Furukawa and coworkers synthesized some imidazole derivatives that specifically block the Ang II-induced vasoconstriction. Important chemical modifications of these initial molecules were then performed with the goal of obtaining an orally active nonpeptide Ang II receptor antagonist. This research led to the synthesis of DuP 753. This compound turned out to be a nontoxic and potent antagonist of Ang II when given orally to animals. The purpose of the present study was to assess for the first time the pharmacokinetic and pharmacodynamic profiles of DuP 753 after single and repeated oral administrations to normal human subjects. The results of this evaluation suggest that DuP 753 is a potent and long-acting antagonist of Ang II, not only in animals but also in humans.

Methods

Subjects

A total of 37 male subjects were recruited to carry out the two consecutive studies.

The first study involved eight volunteers 21–27 years old (mean age, 24 years) and weighing 61–83 kg (mean weight, 73 kg). The second study involved 29 volunteers 20–38 years old (mean age, 25 years) and weighing 53–87 kg (mean weight 70 kg). All subjects were considered healthy on the basis of a medical history, a physical examination, routine blood and urine analyses, and an electrocardiogram. The study protocols were approved by the institutional ethics committee. The nature, purpose, and potential risks of the study were explained to each volunteer, and written consent was required for entry into the study.

Blood Pressure Measurement

In both studies, to quantitate the pressor effect of exogenous angiotensin, blood pressure was measured at the finger using a photoplethysmograph (Finapres, Ohmeda, Englewood, Colo.). The measurement technique is based on the principle of the unloaded artery wall and was first described by Penaz in 1973. This noninvasive method measures finger arterial blood pressure continuously through a cuff wrapped around a finger. The monitor gives a beat-to-beat value of blood pressure (systolic, diastolic, and mean) and heart rate. Shortly before and during the 15 minutes after injection of each test-dose of angiotensin, the pressure waves and heart rate were continuously recorded on graduated paper. The peak blood pressure changes were calculated using these tracings.

Study Outline

Throughout the study, the volunteers were allowed to continue their usual free sodium intake. They were asked to come to our research facility at 7:00 AM on the first day of the study after an overnight fast. They were immediately placed in supine position, and venous catheters were inserted in a vein in each forearm. One line was used for angiotensin injections, and the other for blood sampling. The blood pressure–monitoring cuff was wrapped around the third or fourth finger on the side used for blood sampling.

Study 1 (single-dose study). After a 30-minute resting period to reach a steady baseline blood pressure and heart rate, a dose–response curve to bolus injections of Ang I was established. The goal was to obtain a test-dose able to increase systolic blood pressure by 25–40 mm Hg. Ang I (Senn Chemicals, Dielsdorf, Switzerland) was dissolved in 0.9% NaCl to achieve a concentration of 1 μg/ml. The bolus injections were started at a dose of 10 ng/kg and increased thereafter every 10–15 minutes by increments of 10 ng/kg until the required blood pressure increase was reached. This test-dose was then repeated at least twice. The systolic blood pressure responses to these three consecutive injections of the test-dose were averaged, and the resulting mean was used to define the baseline response to Ang I.

DuP 753 is the potassium salt of 2-n-butyl-4-chloro-5-hydroxyethyl-1-[(2′-1H-tetrazol-5-yl)-biphenyl-4-yl]methylimidazole (E.I. du Pont de Nemours & Co., Wilmington, Del.). It was provided in powder form. The dose to be administered was dissolved in 20 ml of tap water and swallowed by the volunteer, followed by another 100 ml of tap water. The effect of the drug was then monitored using bolus injections of the Ang I test-dose at 15, 30, and 45 minutes and 1, 1½, 2, 2½, 3, 4, 5, 6, 7, 13, 23, 25, and 27 (up to 33 hours for the 40-mg dose) hours after drug intake. Between hours 7 and 12 and again between hours 13 and 22, the subjects were allowed to leave the clinic. The 2-day protocol was repeated four times in each volunteer (except for one volunteer who had only three phases); at each phase, a different dose of drug or placebo was given in single-blind fashion. Placebo was administered to six volunteers. The active drug was administered at doses of 2.5 mg (n = 2), 5 mg (n = 2), 10 mg (n = 6), 20 mg (n = 8), and 40 mg (n = 7). At the end of each phase, routine clinical and laboratory safety evaluations were carried out.

Study 2 (multiple-dose study). During the multiple-dose study, each subject received on the mornings of
eight consecutive days one dose of DuP 753 (5, 10, 20, or 40 mg) or placebo. Thus, each dose or placebo was given in single-blind fashion to six subjects, except the 20-mg dose, which was received by only five volunteers. In this second study, Ang II was used for the challenge. Ang II (Senn Chemicals) was dissolved in 0.9% NaCl to achieve a concentration of 1 μg/ml. Aliquots of Ang II were prepared for each subject in an amount sufficient to cover the needs of the entire study, and for every new day of Ang II challenging, a new aliquot was used. The dose–response curve to establish the test-dose of Ang II was carried out during the week preceding the first administration of DuP 753 using the procedure described above. During study days 1–9, the subjects came every day at 8:00 AM and 6:00 PM to the research facility for measurement of sitting and standing blood pressure (by a sphygmomanometer), heart rate, and weight. On study days 1–8, the dose of DuP 753 or placebo was administered at 8:00 AM, similar to the single-dose study. On days 1, 4, and 8, an Ang II challenge was performed before and again 6 and 12 hours after drug intake. Additional test-doses were injected 24 hours after drug on day 1 as well as 24, 30, and 36 hours after the last dosing on day 8. At the end of the study, all volunteers underwent the same safety evaluations as in study 1.

**Neurohumoral Variables**

In the first study, plasma aldosterone, norepinephrine, and immunoreactive Ang II were measured before and ½, 2, 4, 7, and 23 hours after drug intake. During the second study, plasma renin activity (PRA) was determined with the same parameters on days 1, 4, and 8 before and 6 hours after dosing. In both studies, blood samplings were always performed immediately before the following angiotensin challenge. Aldosterone was determined by a direct radioimmunoassay. For the measurement of PRA, generated Ang I was trapped and quantitated by high-affinity antibodies. For the quantitation of immunoreactive Ang II, a new method using monoclonal antibodies against Ang II was used. Antibodies did not show any cross-reaction with DuP 753 when tested up to a 10-fold excess compared with angiotensin. Norepinephrine was measured by a radioenzymatic assay. Subjects remained in a supine position for 30 minutes before blood sampling.

**Plasma Drug Levels**

Plasma levels of DuP 753 were determined by a high-performance liquid chromatography method. Briefly, plasma standards or samples spiked with an internal standard, 1 ml H₂O, 0.3 ml of 0.1N KOH, and 0.25 ml of 10 mM tetrabutylammonium hydrogen sulfate were extracted with 8 ml methylene chloride. An aliquot of the organic phase was evaporated under a stream of nitrogen, the residue was reconstituted with 0.2 ml of mobile phase, and an aliquot (0.1 ml) was analyzed using a Zorbax R C-8 4.6 mm x 25 cm column (E.I. du Pont de Nemours). Detection was accomplished using an ABI 783A ultraviolet detector (Applied Biosystems, Foster City, Calif.) set at 254 nm. The coefficient of variation of the in-study quality control plasma sample (9.9–183.2 ng/ml) ranged from 4.4% to 9.9%. The accuracy (found concentration divided by spiked concentration) was established by recovery standards (9.9–183.2 ng/ml) and ranged from 91.7% to 97.3%.

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**Table 1. Supine Finger Blood Pressure and Heart Rate Before and After Angiotensin I Challenges and Before and After Single Doses of DuP 753 or Placebo**

<table>
<thead>
<tr>
<th>Time after drug intake (hr)</th>
<th>Before angiotensin I</th>
<th>After angiotensin I</th>
<th>Systolic blood pressure increase (mm Hg)</th>
</tr>
</thead>
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<td>Heart rate (beats/min)</td>
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</tr>
<tr>
<td>Placebo (n=6)</td>
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<td>151/95±4/3</td>
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<tr>
<td></td>
<td>118/69±4/3</td>
<td>57±3</td>
<td>147/94±4/3</td>
</tr>
<tr>
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<td>148/94±3/2</td>
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<td>142/88±3/3</td>
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<td>56±2</td>
<td>129/75±5/3</td>
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Values are given as mean±SEM. 
⁎p<0.01.
TABLE 2. Supine Finger Blood Pressure and Heart Rate Before and After Angiotensin II Challenges and Before and During 8 Days of Administration of Different Doses of DuP 753 or Placebo

<table>
<thead>
<tr>
<th>Day of and time after drug intake</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Systolic blood pressure increase (mm Hg)</th>
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<td></td>
<td>Before angiotensin II</td>
<td></td>
<td>After angiotensin II</td>
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<tr>
<td>Placebo (n=6)</td>
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<td>1/0</td>
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<td>147/89±3/2</td>
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<td>28±2</td>
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<td>4/0</td>
<td>118/61±5/2</td>
<td>54±2</td>
<td>146/85±3/2</td>
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<td>28±3</td>
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<td>140/81±4/4</td>
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<td>145/87±4/3</td>
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<td>142/86±4/2</td>
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<td>148/87±8/4</td>
<td>43±4</td>
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<td>4/0</td>
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<td>DuP 753 40 mg (n=6)</td>
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<td>1/0</td>
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</table>

Values are given as mean±SEM.
*p<0.01, t<0.05.

ranged from 100.3% to 115.4%. The lower quantifiable limit was 8 ng/ml.

Statistical Analysis

All values are provided as mean±SEM unless otherwise indicated. The data were evaluated with a one-way analysis of variance model. Changes in blood pressure and heart rate after angiotensin challenges were calculated for each patient at each dose and at each time before and after drug or placebo intake by taking the difference between the values before and after challenge. Each dose/time mean was tested for significant difference from the corresponding placebo/time mean by the least significant difference method. For the humoral measurements, the identical approach was used. A probability value of less than 0.05 was considered significant. The correlation coefficients were calculated when indicated by the method of least squares.

Results

Safety of Single and Multiple Oral Doses of DuP 753

No clinically significant adverse reaction was observed in any of the volunteers during either study. DuP 753 had no effect on blood pressure and pulse rate after single administration as well as after the 8-day treatment, at rest (Tables 1 and 2). In the single-dose study, three subjects reported some transient tachycardia after moderate exercise. In the multiple-dose study, no such episode was observed by any of the volunteers. Blood counts, routine laboratory tests, urine analyses, and electrocardiograms were also not modified by DuP 753.

Effect of a Single Dose of DuP 753 on Blood Pressure Response to Ang I

The values of blood pressure and heart rate before and after (peak values) Ang I challenge are summarized in Table 1. The changes in systolic blood pressure induced by the test-dose of Ang I were calculated as the differences between postchallenge and prechallenge values for each volunteer at each dose and at each time. Compared with placebo, no clear effect was observed with the doses of 2.5 and 5 mg. However, doses of 10, 20, and 40 mg induced a dose-dependent inhibition of the response to Ang I. Figure 1 shows the dose-related inhibition of the response to Ang I expressed in percent of the baseline response. The peak inhibitory effect was reached 7.5, and 3 hours after intake of the 10-, 20-, and 40-mg doses of DuP 753, respectively. After a dose of 20 mg DuP 753, the blood pressure response to Ang I was decreased to 50%, whereas after the 40-mg dose it decreased to a level of 31%. An attenuation of the blood pressure response to Ang I was still present 24 hours after intake of the 20- and 40-mg doses.

Effect of 8-Day Treatment With DuP 753 on Blood Pressure Response to Ang II

Compared with placebo, the 8-day treatment with DuP 753 taken once a day resulted in a dose-
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.

dependent reduction in the systolic blood pressure response to Ang II throughout the treatment period. Although placebo did not alter the response to exogenous Ang II, the degree of blockade achieved with the 20- and 40-mg doses was similar 6 hours after drug intake on days 1, 4, and 8 (p<0.01 for effect of DuP 753 versus placebo). On days 4 and 8, however, the subjects receiving 40 mg DuP 753 showed a clear trend toward a reduced response to exogenous Ang II immediately before the morning dose of the drug (Table 2 and Figure 2). Figure 3 illustrates the effect of placebo and of the 20- and 40-mg doses of DuP 753 on the responses to Ang II test-dose expressed in percent of the baseline response throughout the treatment period. The data of all five groups (treated with either placebo or 5, 10, 20, or 40 mg DuP 753) are summarized in Figure 4, which provides the pressure response to Ang II.

Figure 2. Plots of individual systolic blood pressure (SBP) responses to test-doses of angiotensin II (ANG II) observed before beginning and at end of 8 consecutive days of treatment with placebo or oral DuP 753 (40 mg p.o. o.d.). C, control before ANG II injections; All, after ANG II injections; D, days; H, hours.

Figure 3. Plots of effects of 8 consecutive days of treatment with two oral doses of DuP 753 (20 or 40 mg p.o. o.d.) or placebo on systolic blood pressure (SBP) response (mean) to test-doses of angiotensin II (ANG II) in healthy volunteers.

Figure 4. Bar graphs of systolic blood pressure (SBP) responses induced by test-doses of angiotensin II (ANG II) before and 6 hours after drug on days 1, 4, and 8 of treatment with four different doses of DuP 753 (5, 10, 20, or 40 mg p.o. o.d.) or placebo (n=6 for each dose except dose of 20 mg, where n=5). Values are given in mean±SEM.
Figure 5. Plots of effects of single doses of oral DuP 753 (10, 20, or 40 mg p.o.) 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±SEM.

expressed in percent of baseline before and 6 hours after DuP 753 intake for days 1, 4, and 8.

Effect of DuP 753 on Neurohumoral Variables

Study 1. Plasma aldosterone levels decreased after administration of single doses of DuP 753, but a similar decrease was also seen after placebo (Figure 4, lower panel). Compared with placebo, the single doses of DuP 753 had no effect on urinary sodium excretion (not shown). The single doses of DuP 753 produced a dose-dependent increase in plasma Ang II, whereas no change was observed after placebo administration. As early as 30 minutes after the highest dose (40 mg), a small increase was apparent, the peak level of 12.7±2.1 fmol/ml (p<0.05 versus placebo) being reached 7 hours after dosing (Figure 5, upper panel). No significant change in plasma norepinephrine was observed after single administration of DuP 753 (not shown).

Study 2. Figure 6 depicts the PRA and plasma Ang II levels measured at the beginning and end of repeated administration of placebo or DuP 753. Both PRA and Ang II showed a marked dose-dependent increase 6 hours after drug intake, and this increase was clearly more pronounced on day 8 than on day 1. Both variables had already increased significantly 6 hours after administration of 20 mg DuP 753 on the first day (p<0.05 versus placebo). Although the baseline results on day 1 were very similar, on day 8 there was a trend for a dose-dependent increase of even the predrug values.

A close correlation was found between PRA and plasma Ang II (r=0.96, n=116, p<0.001). There was also a negative correlation between the increase in PRA and the systolic blood pressure response to exogenous Ang II (r=-0.61, n=116, p<0.001). Neither plasma norepinephrine (not shown) nor plasma aldosterone (not shown) changed during the 8-day administration of DuP 753.

Plasma Concentrations of DuP 753 and Pharmacokinetic Parameters

Peak plasma levels of DuP 753 were reached 30 minutes after drug intake with all doses tested (10, 20, and 40 mg). Then, the drug concentrations decreased progressively and became undetectable between hours 5 and 13 after drug intake. The drug half-life was estimated for all subjects as between 1.5 and 3.3 hours (2.1±0.6 hours, mean±SD). Figure 6 depicts the time courses of the drug levels and the corresponding inhibitions of the systolic blood pressure responses to Ang I (upper panel). In the lower panel of this figure, the time course of the drug levels is given with the plasma Ang II concentrations measured after administration of the single doses of DuP 753 (20 and 40 mg). There was a pronounced shift in time between the peak drug level and the peak inhibitory effect reflected by either inhibition of the Ang I pressure response or the compensatory increase in plasma Ang II levels. Furthermore, the inhibition of the response to Ang I as well as the increase in plasma Ang II were still present when the drug became undetectable in plasma. When the individual plasma drug levels were related to the concomitant plasma Ang II or the reduction in the Ang I-induced pressure response, there was no detectable correlation.

Discussion

It has recently become possible to characterize compounds such as ACE and renin inhibitors with progressively increasing degrees of accuracy by quantitating their effects on plasma ACE activity and/or Ang II. The determination of true angiotensin-(1-8)-octapeptide is probably the best index by which to assess blockade of the renin-angiotensin enzymatic cascade. In contrast, the only practical way to estimate the effect of an Ang II receptor antagonist in a clinical setting is to monitor its inhibitory effect on the blood pressure response to exogenous Ang I or II. Until recently, a direct measurement of intraarterial blood pressure was necessary for the detection of the rapid blood pressure increase induced by the bolus injection of a pressor substance such as Ang I or II. However, intra-arterial catheterization involves a certain risk. Consequently, this approach was limited to studies of very small numbers of subjects, lasting for not more than a few hours. The recent development of a servophotoplethysmograph able to monitor blood pressure at the finger continuously
and noninvasively made the present study possible, which we could not have carried out a few years ago. In a pilot study performed in six normal subjects, the reproducibility of the systolic pressure response to repeated administration of an Ang I test-dose was evaluated over a period of 24 hours, and the mean coefficient of variation was found to be 15±2.4% (mean±SEM; range, 11–24%). Furthermore, the administration of captopril at doses of 6.25 and 25 mg p.o. reduced the response to Ang I in a pattern that confirmed the results obtained almost 15 years ago with intra-arterial blood pressure monitoring. Based on these preliminary results and on similar experiences reported recently by others, it was decided that the photoplethysmographic blood pressure method could be used to assess the efficacy of DuP 753 in normal volunteers.

The present data demonstrate that DuP 753 is a potent, orally active Ang II antagonist with a relatively long duration of action. At peak effect, the 40-mg dose induced an approximately 70% reduction in the systolic pressure response to Ang I or II. In addition, with this highest dose, even 24 hours after drug intake, a definite blocking effect was still present. Notwithstanding, with repeated administration, no cumulative progressive enhancement of the blocking effect 6 hours after drug could be observed. The dose–response relation that was observed with the blocking effect of the angiotensin–induced pressure response was also clearly reflected in the compensatory increase in PRA and immunoreactive Ang II.

Although the different effects induced by the administration of the Ang II antagonist were clearly long lasting, the actual drug levels in plasma had relatively short half-lives varying between 1.5 and 3.3 hours in the individual subjects. Furthermore, there was no correlation between the individual plasma drug levels and the concomitant plasma Ang II or blockade of the Ang I–induced blood pressure response. These data quite strongly suggest that DuP 753 in its intact form is not the major active component responsible for the inhibitory action and that possibly some active metabolite exists in man. In animal experiments, metabolism of DuP 753 has been demonstrated, and an active metabolite has been identified. It is thus probable that in humans, as in animals, DuP 753 is metabolized and that the main inhibitory action is exerted by one or more active metabolites.

PRA and Ang II levels responded with dose-dependent compensatory increases as might have been expected based on earlier observations made with saralasin, the analogue of Ang II used as an Ang II antagonist, as well as on the extensive experience accumulated with ACE inhibitors. Not only was this compensatory increase dose dependent, but there also was a clear time factor (i.e., on day 8 of drug administration, the compensatory increase was clearly more pronounced than on day 1). This also is in agreement with findings obtained after administration of ACE inhibitors. The long duration of the blocking effect of DuP 753 is also reflected in the PRA and Ang II levels. Thus, although on day 1 all predrug measurements provided similar results, on day 8, PRA as well as plasma Ang II were clearly increased before the administration of 20 or 40 mg compared with the predrug results obtained before placebo. Thus, 24 hours after the administration of 20 or 40 mg, there was still a significant compensatory increase in PRA and Ang II present. An important question is, of course, whether this compensatory increase in plasma Ang II levels can modify the inhibitory effect of the DuP 753. At the outset of the study, it was hoped that by measuring circulating Ang II and plasma drug levels while simultaneously evaluating the drug effect on the pressure response to Ang II, it would be possible to assess the influence of the increasing Ang II levels. Unfortunately, this was not possible because the measured drug levels do not appear to represent the main inhibitory compound.

No clear effect of the Ang II antagonist on plasma aldosterone could be detected. Had there not been a

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Bar graphs of effects of four different doses of DuP 753 (5, 10, 20, or 40 mg p.o. o.d.) 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 hours after drug intake on days 1 and 8. Values are given as mean±SEM. *p<0.05, **p<0.01 vs. placebo.
placebo administration included in the study, it would have been concluded that DuP 753 reduces plasma aldosterone at 10-, 20-, and 40-mg doses. Because a similar decrease in plasma aldosterone was observed after placebo administration, this decrease in aldosterone levels is probably related to the circadian rhythm of aldosterone secretion. The same kinds of observations have been made in normal volunteers after acute ACE inhibition. The decrease in plasma aldosterone levels were parallel in subjects who received the placebo and in those treated with different doses of the active compound. There are many other possible reasons why no net effect of the drug on plasma aldosterone could be demonstrated. Most important, it has to be kept in mind that the 40-mg dose does not appear to provide maximal receptor blockade. Although this was true for the vascular receptors, the degree of blockade at the adrenal receptor might have been considerably less. Furthermore, for testing purposes, repeat Ang I or II bolus injections were administered. It is thus conceivable that these bolus injections of Ang I or II in the face of incomplete receptor blockade may have exerted a significant stimulating effect on aldosterone secretion.

The clinically most relevant question, of course, is how DuP 753 as a therapeutic agent compares with the various agents currently available for blockade of the renin-angiotensin cascade. Obviously, results from the present study cannot provide any conclusive answer to this question because the drug was administered only to normal volunteers. Nevertheless, it is already evident that this Ang II antagonist exhibits features that make it appear particularly promising as a future therapeutic agent. Compared with saralasin, it has the evident and decisive advantage of being orally active. Furthermore, although the present data cannot rule out the existence of an agonistic effect of DuP 753 because relatively small doses were administered, it seems likely that no such effect will occur in humans because none was observed at very high doses of drug in various animal studies.

By far the largest experience available with agents blocking the renin-angiotensin system is with ACE inhibitors. For several reasons, it is very difficult to make any comparison with ACE inhibitors because when administered at therapeutic doses, these agents can reduce both plasma ACE activity and plasma angiotensin-(1-8)-octapeptide levels by 80% or more. The measurement of these plasma variables in normal volunteers after administration of ACE inhibitors has therefore made it possible to predict the dose of the inhibitor necessary to provide a full antihypertensive effect of the drug. DuP 753 given at a dose of 40 mg reduced the Ang II–induced blood pressure effect by only 70%. Clearly, the present study does not provide a full range of the dose–response curve to DuP 753. It is thus possible that higher degrees of blockade will be necessary for adequate therapeutic efficacy; accordingly, higher doses will have to be administered. Based on observations made in animal experiments, it is known that close-to-complete blockade of the Ang II pressure response can be obtained.

Even if a full dose–response curve to DuP 753 in humans were available, the comparison with a converting enzyme inhibitor would still be difficult. Although we have learned over the years that true Ang II levels have to be reduced markedly to obtain a good antihypertensive effect, we presently have little idea what percentage of Ang receptors on the smooth muscle cells of the arterioles have to be occupied by an Ang II antagonist to obtain a partial or maximal antihypertensive effect. The Ang II bolus doses used for testing in the present study induced, for a short period of time, much higher Ang II levels than are usually present at the angiotensin receptor site. Accordingly, even though the 40-mg dose of DuP 753 appears to provide only partial blockade of the pressure response to exogenous Ang I or II, it might represent a full or even excessive antihypertensive dose. Only when data become available from hypertensive patients studied under well-controlled conditions will it be possible to extrapolate from the degree of blockade measured in normal volunteers the doses necessary for a full antihypertensive effect in hypertensive patients.

Based on these preliminary data obtained in normal volunteers, it is not possible to predict the antihypertensive potency and efficacy of DuP 753. Nevertheless, the findings obtained with DuP 753 in
hypertensive animals and the earlier observations made with saralasin suggest that DuP 753 will probably become an effective compound to treat hypertension and possibly congestive heart failure. Compared with ACE inhibitors, it would have the advantage of greater specificity. It shares with the ACE inhibitors as well as with the renin inhibitors the inescapable fact that the closed regulatory loop of renin secretion is fully operative; as a consequence, blockade at any point beyond the renin-secreting process automatically induces compensatory increases in renin and Ang II. Whether this compensatory increase has any clinical consequences remains to be seen.

References


**Key Words**
- photoplethysmography, finger
- angiotensin II
- clinical trials
- DuP 753
Oral administration of DuP 753, a specific angiotensin II receptor antagonist, to normal male volunteers. Inhibition of pressor response to exogenous angiotensin I and II.
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