(*Hypertension.* 1995;25:22-29.)

Articles

Hemodynamic and Biochemical Effects of the AT_1 Receptor Antagonist Irbesartan in Hypertension

Anton H. van den Meiracker; Peter J.J. Admiraal; Joop A. Janssen; Jan-Maarten Kroodsma ; Wijnand A.M. de Ronde; Frans Boomsma; Joëlle Sissmann; P.J. Blankestijn; Paul G.M. Mulder ; Arie J. Man in `t Veld; Maarten A.D.H. Schalekamp

From the Department of Internal Medicine I, University Hopital Dijkzigt, Rotterdam (A.H. van den M., P.J.J.A., J.A.J., F. B., A.J.M.V., M.A.D.H.S.); U-Gene Research BV, Utrecht (J.-M.K., W.A.M. de R.), the Netherlands; Sanofi Recherche, Montpellier, France (J.S.); the Department of Nephrology, University Hospital Utrecht (P.J.B.); and the Department of Epidemiology and Biostatistics, Erasmus University Rotterdam (P.G.M.M.).

Abstract

Abstract We studied the hemodynamic, neurohumoral, and biochemical effects of the novel angiotensin type 1 (AT_1) receptor antagonist irbesartan in 86 untreated patients with essential hypertension on a normal sodium diet. According to a double-blind parallel group trial, patients were randomized to a once-daily oral dose of the AT_1 receptor antagonist (1, 25, or 100 mg) or placebo after a placebo run-in period of 3 weeks. Randomization medication was given for 1 week. Compared with placebo, 24-hour ambulatory blood pressure did not change with the 1-mg dose, and it fell (mean and 95% confidence interval) by 7.0 (4.2-9.8)/6.1 (3.9-8.1) mm Hg with the 25-mg dose and by 12.1 (8.1-16.2)/7.2 (4.9-9.4) mm Hg with the 100-mg dose. Heart rate did not change during either dose. With the 25-mg dose, the antihypertensive effect was attenuated during the second half of the recording, and with the 100-mg dose, it was maintained for 24 hours. Baseline values of renin and the antihypertensive response to the 25- and 100-mg doses were well correlated (r=.68, P<.01). Renin did not change with the 1-mg dose, but it rose threefold to fourfold with the 25-mg dose and fourfold to fivefold with the 100-mg dose 4 to 6 hours after administration. With the 100-mg dose, renin was still elevated twofold 24 hours after dosing. The changes in renin induced by the AT_1 receptor antagonist were associated with parallel increments in angiotensin I and angiotensin II. Aldosterone, despite AT_1 receptor blockade, did not fall.

Compared with baseline values, plasma norepinephrine increased moderately with the 100-mg but not with 25- or 1-mg dose. Serum uric acid and its 24-hour urinary excretion did not change. In conclusion, in essential hypertension, once-daily irbesartan effectively lowers blood pressure. This effect is maintained for 24 hours with a 100-mg dose. Unlike the AT_1 receptor antagonist losartan, irbesartan exerts no uricosuric effect, suggesting that this is an effect unrelated to AT_1 receptor blockade.

Key Words: receptors, angiotensin • hypertension, essential • hemodynamics • renin • angiotensin I • angiotensin II • aldosterone • norepinephrine • uric acid

Introduction

Top
Abstract
Introduction
Methods
Results
Discussion
References

The beneficial results obtained with angiotensin-converting enzyme (ACE) inhibitors in the management of hypertension and congestive heart failure have stimulated the search for other approaches for pharmacological interference with the renin-angiotensin system. Most promising in this respect so far is the development of orally active, nonpeptide, competitive antagonists for the angiotensin II (Ang II) receptor, of which losartan was the first to be used in clinical studies.[1] [2] [3] [4]

In addition to losartan, a number of other orally active nonpeptide Ang II receptor antagonists have been developed.[5] Irbesartan (SR 47436, BMS 186295) is one of these agents. Like losartan, this novel compound is a selective antagonist for the Ang II type 1 (AT_1) receptor.[6] The irbesartan concentration needed to reduce specific binding of ^{125}I-Ang II to rat adrenal cortical microsomes by 50% is 0.9 nmol/L,[5] whereas for losartan and its active metabolite EXP 3174, these values are 5.5 and 1.3 nmol/L, respectively.[5] Irbesartan, unlike losartan, has no active metabolite.[6]

In healthy volunteers, single doses (5 to 400 mg) and repeated doses (5 to 200 mg for 7 days) of oral irbesartan once daily caused dose-dependent increases of renin and Ang II but had no effect on blood pressure (BP).[7] With the higher doses (25 to 200 mg), increases of renin and Ang II were still present 24 hours after administration, suggesting a long duration of action. This was confirmed by studies evaluating the inhibitory effect of single oral doses of the compound on the pressor effect of intravenous bolus injections of Ang II in healthy volunteers. Compared with placebo, the pressor effect of Ang II after a 5-mg dose of irbesartan was blunted by 50% from 2 to 8 hours after administration. After a 25-mg dose, significant inhibition of the pressor effect was maintained for 24 hours and after 50- and 100-mg doses even for 36 hours (data on file, Sanofi Recherche, Montpellier, France).

The present study is the first detailed evaluation of the hemodynamic, neurohumoral, and biochemical effects of three different doses (1, 25, and 100 mg) of irbesartan in patients with essential hypertension.

Methods

Top
Abstract
Introduction
Methods
Results
Discussion
References

Patients

Male and postmenopausal or surgically sterilized female patients with mild to moderate essential hypertension (diastolic BP, Korotkoff phase V, between 95 and 115 mm Hg after 2 weeks' washout of all antihypertensive medications) on a normal sodium diet were eligible to participate in the study if their age was between 18 and 70 years and if they were willing to give written informed consent. Secondary forms of hypertension were excluded by clinical and laboratory evaluation. Patients with cardiovascular diseases —including stroke, cardiac failure, angina pectoris, and rhythm disturbances on electrocardiogram—and clinically relevant respiratory, endocrine, gastrointestinal, renal, or hepatic abnormalities were excluded from the study.

The study was performed at two centers: the Department of Internal Medicine I of the University Hospital Dijkzigt in Rotterdam (center 1) and the center

for clinical research U-Gene BV in Utrecht (center 2). In total, 105 patients entered the study.

Design

The study was carried out according to a double-blind, placebo-controlled, parallel-group design. After a 2-week period during which all patients were off antihypertensive medication, placebo (single-blind, once daily) was given for 3 weeks. During this period, the patients were seen at weekly intervals. At each visit, they were asked about symptoms, and BP was measured by standard mercury sphygmomanometry after a 45-minute period of supine rest. BP and heart rate were measured three times with patients in the supine and two times in the erect positions (first measurement after 1 minute of standing). At the end of the 3-week single-blind placebo period, the patients had their first study day. On this day they arrived at 7:30 AM at the research laboratory. After arrival, an intravenous cannula for blood sampling was introduced into a forearm vein, and equipment for 24-hour ambulatory BP monitoring (model 90207, SpaceLabs Inc) was fitted to the patients. Ambulatory BP was measured in the nondominant arm. From 7 AM to 8 PM, ambulatory BP was measured at 15-minute intervals and from 8 PM to 7 AM at 30-minute intervals.

At time 0 and 1, 2, 4, 6, 10, and 24 hours after study medication, blood for measurement of Ang I, Ang II, renin, aldosterone, and catecholamines was collected. At 24 hours, blood was also collected for routine hematologic (complete blood count) and biochemical (urea nitrogen, creatinine, total bilirubin, alanine and aspartate transferases, alkaline phosphatase, lactate dehydrogenase, glucose, cholesterol, total protein, sodium, potassium, chloride, uric acid, calcium, and inorganic phosphorus) measurements. Blood sampling was performed after patients had rested in the supine position for 20 minutes. After blood sampling, supine and erect BPs were measured by standard mercury sphygmomanometry in a manner similar to that of the single-blind placebo period. During the study day, urine was collected for measurement of the 24-hour urinary excretion of creatinine, sodium, and uric acid. If at the end of the single-blind placebo period patients still fulfilled the entry criteria, they were randomized for one of the doses (1, 25, or 100 mg) of the AT_1 receptor antagonist or placebo and entered the double-blind phase of the study. The 1-mg dose was included for the sake of obtaining information about a "no-effect dose" of this new compound in the target population of hypertensive patients. After 1 week of randomization treatment, the patients had their second study day. During this day, the procedures and measurements were similar to those during the first study day. In addition, at 0, 1, 2, 4, 6, 10, and 24 hours, blood was sampled for assay of plasma drug concentrations.

The study protocol was approved by the Medical Ethics Committees of the two study centers.

Study Medication

During the 3-week single-blind placebo and 1-week double-blind randomization periods, the patients had to take four capsules each morning. Treatment boxes (one for each week) contained nine sachets with four capsules in each. At each weekly visit, the patients were provided with one box for the corresponding period. Adherence to medication was checked by counting the capsules returned by the patients. The randomization medication of period 4 consisted of either placebo or 1 mg (one capsule with 1-mg irbesartan and three placebo capsules), 25 mg (one capsule with 25 mg irbesartan and three placebo capsules), or 100 mg (four capsules of 25 mg irbesartan) of the AT_1 receptor antagonist. During the 2 study days, the patients took their medication in the cardiovascular laboratory at time 0 after withdrawal of the first blood sample.

Analytical Methods

For plasma active renin concentration, 5 mL blood was collected in tubes containing 0.1 mL of 0.7 mol/L sodium citrate. Samples were centrifuged at 3000*g* for 10 minutes at 4°C, and plasma was stored at -20°C. Plasma renin concentration was measured as the rate of Ang I formation during incubation of plasma with saturating amounts of sheep renin substrate at 37°C and neutral pH.[8] Plasma total renin concentration was measured in a similar way after activation of plasma inactive renin with trypsin-Sepharose for 48 hours at 4°C. Plasma inactive renin concentration (prorenin) was measured by subtracting the active renin concentration from the the total renin concentration. The Ang I formed by the reaction of renin with sheep renin substrate was measured by radioimmunoassay. Plasma renin concentration was expressed in milliunits per liter with the World Health Organization renin standard 68/356 (World Health Organization, International Laboratory for Biological Standards, London, UK) as the reference standard. The lower limit of detection for plasma renin is 0.5 mU/L.

For the measurement of plasma Ang I and Ang II, 5 mL blood was withdrawn with syringes containing 0.3 mL of an inhibitor solution containing 5 µmol/L of the renin inhibitor Ro 42-5892, 10 µmol/L of the ACE inhibitor lisinopril, and 10 mmol/L disodium EDTA. After withdrawal, the blood samples were immediately transferred to prechilled polystyrene tubes and were centrifuged at 3000*g* for 10 minutes at 4°C. Plasma samples were quickly frozen and stored at -70°C. Plasma samples (2 mL) were extracted with SepPak C18 cartridges (Waters Associates Inc) as described previously.[9] Bound angiotensins were eluted with 2 mL methanol, and plasma extracts were evaporated under reduced pressure in a SpeedVac (Savant Instruments). Dried extracts were stored at -20°C until assay. Immunoreactive angiotensins were measured by radioimmunoassay. Immunoreactive Ang I was measured with a polyclonal antiserum (No. 692) produced in our laboratory.[9] The cross-reactivity of this antiserum with Ang II is less than 0.1%. The lower limit of detection of immunoreactive Ang I is 1.2 fmol per tube. Immunoreactive Ang II was measured with a polyclonal antiserum (No. 923) produced by F. Hoffmann–La Roche Ltd.[10] The cross-reactivity of this antiserum with Ang I is less than 0.37%. The lower limit of detection is 0.5 fmol per tube.

For the measurement of plasma catecholamines and aldosterone, 5 mL blood was collected in chilled heparinized tubes containing 6 mg glutathione. Samples were centrifuged immediately at 3000*g* for 10 minutes at 4°C. Plasma was stored at -70°C until assay. Plasma catecholamines were measured by fluorimetric detection after high-performance liquid chromatographic separation as described previously.[11] Aldosterone was measured by solid-phase radioimmunoassay using a commercially available kit (Coat-a-Count, Diagnostic Products Corp).

For the measurement of plasma concentrations of irbesartan, 5 mL blood was collected in tubes containing EDTA. Samples were centrifuged immediately and plasma stored at -20°C until assay. Plasma drug concentrations were determined by radioimmunoassay (quantitation limit, 0.250 µg/L).

Statistical Analysis

Data are presented as mean values and 95% confidence interval or ranges as indicated. Possible differences of baseline values among the four treatment groups were analyzed by ANOVA. Changes in 24-hour, daytime, and nighttime ambulatory BP among the four treatment groups were analyzed by ANCOVA with the baseline value (mean of the last day of placebo) as the covariate. Pairwise statistical comparison of the three doses of the AT_1 receptor antagonist with placebo were made after application of Dunnett's correction. Comparison of clinic supine and erect BP values and neurohumoral data among the treatment groups was performed using repeated-measures ANOVA with an unrestricted within-subject residual matrix. As explanatory

variables, a within-subject factor time with seven levels, a between-factor group, and their interaction were considered. A value of $P<.05$ was considered statistically significant. Correlation coefficients were calculated by the least-squares method.

Results

Top
Abstract
Introduction
Methods
Results
Discussion
References

Of the 105 patients who entered in the study, 19 had to be withdrawn. The main reason for withdrawal was a fall in diastolic BP below 95 mm Hg during the single-blind placebo period. All of the 86 patients, who were eventually randomized for one of the four treatments, completed the study. Forty-nine patients were studied in center 1 and 37 in center 2. For technical reasons, plasma concentrations of renin and prorenin could be measured only in the samples of the patients studied in center 1.

Table 1 shows demographic characteristics of the four treatment groups. Age and baseline BP and heart rate values in the four treatment groups were similar. The mean body weight of the 100-mg treatment group compared with the other three treatment groups was relatively low. Most likely, the high proportion of women in this group accounted for this difference.

View this table: [in this window] [in a new window]

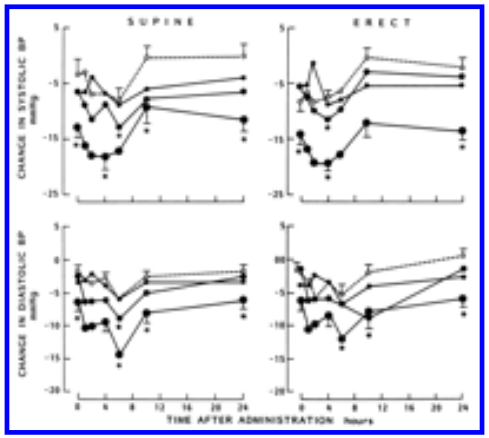
Table 1. Baseline Characteristics of the Four Treatment Groups

The study medication was well tolerated, and no clinically significant adverse reactions occurred in any of the four treatment groups. Routine hematologic and biochemical measurements did not change in response to randomization treatment.

Hemodynamic Effects

BP at the end of the 2-week washout period was 163 (157 to 167) mm Hg systolic and 102 (100 to 104) mm Hg diastolic. Compared with these values, BP did not change significantly during the 3-week single-blind placebo period. Fig 1 shows the changes in supine and erect clinic BP values measured by sphygmomanometer on the second study day (day 7 of randomization treatment) compared with the baseline values of these parameters (average of the measurements during the first study day) for each treatment group. Compared with changes in the placebo group, systolic and diastolic BP values did not change in the 1-mg treatment group. However, compared with the changes in the placebo group, systolic and diastolic BP values were lower ($P<.001$) in both the 25- and 100-mg treatment groups. In the latter treatment group, systolic and diastolic BP values were still significantly reduced by 10.6 (3.3 to 17.9) mm Hg ($P<.001$) and 4.9 (0.1 to 9.6) mm Hg ($P=.016$), respectively, at the end of the dosing interval. Postural hypotension as assessed by the erect

BP measurements did not occur in either the 25- or 100-mg treatment group (Fig 1).

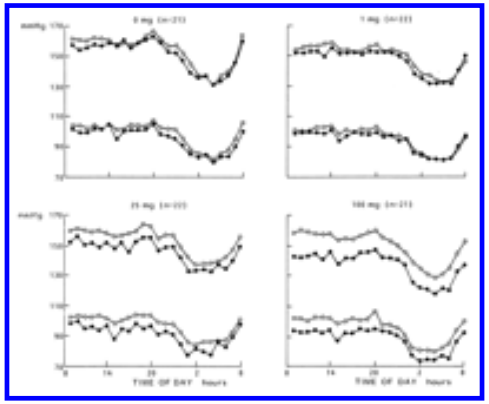


View larger version (29K):
[in this window]
[in a new window]

Figure 1. Line graphs show changes in supine and erect systolic and diastolic blood pressures (BP) at the end of the randomization period in the four treatment groups. Changes compared with baseline BP (average of supine and erect values obtained at the end of the single-blind placebo period) are depicted. Values are mean±SEM. Open circles indicate placebo; small closed circles, 1-mg group; medium closed circles, 25-mg group; and large closed circles, 100-mg group. *P<.05.

Daytime ambulatory systolic and diastolic BP values at the end of the single-blind period were 2.7 (0.5 to 4.9) mm Hg (P=.02) and 2.2 (0.9 to 3.5) mm Hg (P=.03), respectively, lower than clinic baseline supine systolic and diastolic BP values. The two methods of BP measurement were well correlated, with correlation coefficients of .73 (P<.001) for systolic and .66 (P<.001) for diastolic BP.

Fig 2 and Table 2 summarize the results of the 24-hour ambulatory BP recordings. In the placebo treatment group, a small order effect on BP was present. Compared with the first recording, average 24-hour ambulatory systolic BP was 2.6 mm Hg (P=.06) and average 24-hour ambulatory diastolic BP was 3.0 mm Hg (P=.02) lower at the time of the second recording 7 days later. Average 24-hour ambulatory heart rate was 1.4±4.5 beats per minute (P=.16) higher during the second recording. In the 1-mg treatment group, BP on the seventh day of administration did not change compared with placebo values. In the 100-mg treatment group, systolic and diastolic BP values compared with placebo values were lowered throughout the 24-hour period (Table 2). In the 25-mg treatment group, systolic and diastolic BP values also decreased; however, compared with findings in the 100-mg treatment group, the antihypertensive effect was not as long and its magnitude tended to be smaller. The BP-lowering effect was not associated with significant changes in heart rate in either the 25- or 100-mg treatment group (Table 2).



View larger version (25K):
[in this window]
[in a new window]

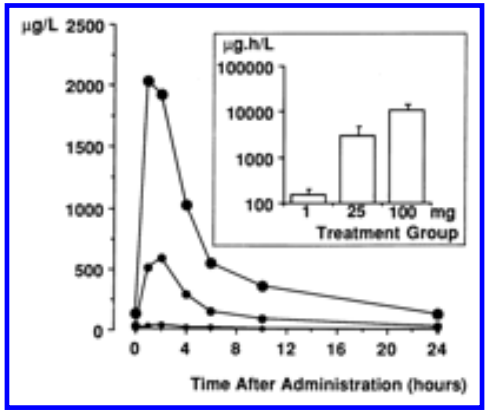
Figure 2. Line graphs show hourly mean values of systolic and diastolic ambulatory blood pressures at the end of the single-blind placebo and randomization periods in the four treatment groups. (◌) indicates placebo; (■), randomization.

View this table:
[in this window]
[in a new window]

Table 2. Changes in 24-Hour, Daytime, and Nighttime Systolic and Diastolic Ambulatory Blood Pressure and Heart Rate Compared With Placebo

Plasma Concentrations of Irbesartan

In the 1-, 25-, and 100-mg treatment groups, peak plasma concentrations of the compound were seen 1 to 2 hours after repeated administration (Fig 3). In the 100-mg treatment group, the maximal plasma concentration was approximately 70 times higher than in the 1-mg treatment group and approximately 3 times higher than in the 25-mg treatment group. Within each treatment group, peak plasma concentrations of irbesartan varied by a factor of approximately 3. The area under the curve of irbesartan was 151 (130 to 175) μg · h/L in the 1-mg group, 2979 (2539 to 3494) μg · h/L in the 25-mg group, and 10 613 (8593 to 13 108) μg · h/L in the 100-mg group. BP changes were notcorrelated with area under the curve values in either the 25- or 100-mg treatment group.



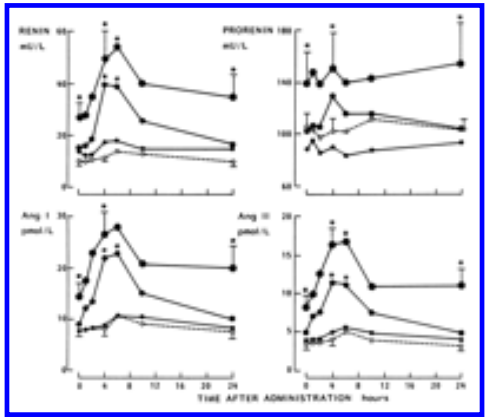
View larger version (24K):
[in this window]
[in a new window]

Figure 3. Line graph shows plasma concentrations of irbesartan at the end of the randomization period. Inset, Bar graph shows area under the curve of the three doses (note logarithmic scale). Small closed circle indicates 1-mg dose; medium closed circle, 25-mg dose; and large closed circle, 100-mg dose.

Effects on Plasma Prorenin, Renin, Ang I, Ang II, Aldosterone, and Catecholamines

Baseline values of plasma prorenin, renin, Ang I, Ang II, and aldosterone obtained during the placebo study day did not differ among the four study groups. Baseline values of plasma renin were well correlated with baseline values of plasma Ang I (n=49, r=.78, P<.001) and Ang II (n=49, r=.85, P<.001).

Compared with the placebo group, no significant changes in any of the hormonal measurements were observed with the 1-mg dose (Fig 4). An increase in prorenin, renin, Ang I, and Ang II occurred in response to treatment with both the 25- and 100-mg doses (Fig 4). With the 25-mg dose, values of prorenin, renin, Ang I, and Ang II at the end of the dose interval had returned to values similar to those seen with placebo, whereas with the 100-mg dose, values remained elevated above placebo values. With both the 25- and 100-mg doses, the maximal increase in renin occurred 4 to 6 hours after administration. With the two doses, the increments in plasma Ang I and Ang II ran in parallel with the increments in renin.

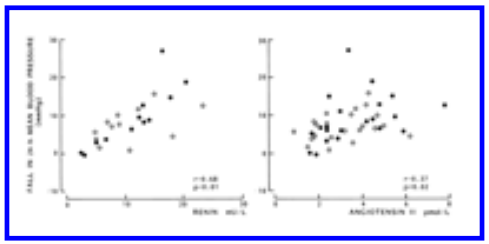


View larger version (26K):
[in this window]
[in a new window]

Figure 4. Line graphs show plasma concentrations of prorenin, renin, and angiotensin (Ang) I and II of the four treatment groups at the end of the randomization period. Values are mean±SEM. Open circles indicate placebo; small closed circles, 1-mg group; medium closed circles, 25-mg group; and large closed circles, 100-mg group. *P<.05 vs changes in 0-mg treatment group.

Plasma aldosterone values compared with those in the placebo group did not change significantly in any of the treatment groups (data not shown).

Pretreatment values of renin and the responses of 24-hour mean BP to the 25- and 100-mg doses of the AT_1 receptor antagonist were well correlated (r=.68, P<.01, n=24), whereas there was little correlation in the responses of 24-hour mean BP and pretreatment values of Ang II (r=.37, P<.02, n=43) (Fig 5).



View larger version (9K):
[in this window]
[in a new window]

Figure 5. Scatterplots show relationship between baseline values of renin or angiotensin II and changes in blood pressure in response to irbesartan. (○) indicates 25-mg dose; (●), 100-mg dose.

Pretreatment values of plasma catecholamines were similar in the four treatment groups (data not shown). Compared with changes in plasma norepinephrine in the placebo group, a small increase in plasma norepinephrine, which was significant only 6 hours after administration, occurred in response to the 100-mg dose. Plasma epinephrine and dopamine did not change in any of the treatment groups.

Effects on Body Weight, Urinary Sodium Excretion, Serum Electrolytes, Renal Function, and Uric Acid

Body weight did not change in any of the four treatment groups. Twenty-four–hour urinary sodium excretion and renal function as estimated by values of serum creatinine and creatinine clearance did not change in response to placebo or the AT_1 receptor antagonist (Table 3). Serum uric acid and relative uric acid clearance also did not change in any of the four treatment groups (Table 3). Baseline values of 24-hour urinary sodium excretion and the antihypertensive response to the 25- and 100-mg doses of the AT_1 receptor antagonist were not correlated.

View this table: [in this window] [in a new window]

Table 3. Body Weight, 24-Hour Urinary Sodium Excretion, Serum Creatinine, Creatinine Clearance, Serum Uric Acid, and 24-Hour Uric Acid Excretion in the Four Treatment Groups Before and After Randomization Period

Discussion

Top
Abstract
Introduction
Methods
Results
Discussion
References

This study is the first evaluation of the hemodynamic and neurohumoral effects of the selective AT_1 receptor antagonist irbesartan (SR 47436, BMS 186295) in patients with mild to moderate hypertension. Of the three once-daily doses (1, 25, and 100 mg) tested, only the 25- and 100-mg doses produced an antihypertensive effect, and only with the 100-mg dose was this effect maintained for 24 hours after a 7-day treatment. Irbesartan did not cause postural hypotension, and its BP-lowering effect was not accompanied by significant increments in heart rate.

Interruption of the renin-angiotensin system by AT_1 receptor blockade is associated with an increase in renin and Ang I and II probably because of withdrawal of the negative feedback of Ang II on the release and synthesis of renin from the juxtaglomerular cells in the kidney.[12] [13] In the present study, a compensatory increase of renin, prorenin, Ang I, and Ang II was observed with both the 25- and 100-mg doses but not with the 1-mg dose. With the 100-mg dose, an increase of the components of the renin-angiotensin system was still present 24 hours after dosing. Therefore, it appears that with respect to duration of action, the dose-dependent effects of irbesartan on BP have their correlate in the compound-induced activation of

the renin-angiotensin system.

Losartan has been shown to lower BP effectively in spontaneously hypertensive rats and in the two-kidney, one clip model of hypertensive rats, but the compound does not have any BP-lowering effect in deoxycorticosterone acetate–salt hypertensive rats or nephrectomized spontaneously hypertensive rats.[14] [15] These experimental studies indicate that the renin or Ang II dependency of BP is the sole determinant of the BP-lowering potential of AT_1 receptor antagonists. The findings of the present study are in line with these experimental data. First, a rather strong relationship between baseline values of renin and the antihypertensive effect of the AT_1 receptor antagonist was observed, and second, no BP-lowering effect in response to either the 25- or 100-mg dose of the AT_1 receptor antagonist was noticed in patients with a relatively low plasma renin concentration. It further appears that in patients with a relatively high plasma renin concentration, a pronounced antihypertensive effect may be obtained with the lower 25-mg dose.

Ang II–induced secretion of aldosterone by the adrenal cortex, like vascular smooth muscle contraction, is also mediated by the AT_1 receptor.[16] [17] [18] We therefore expected to find a decrease in plasma aldosterone concentration during administration of the AT_1 receptor antagonist. This appeared not to be the case, suggesting that in salt-replete patients with essential hypertension, Ang II exerts no important tonic stimulatory effect on aldosterone secretion. Our observation is not unique, because no decrease in plasma aldosterone concentration, despite evidence for AT_1 receptor blockade, has also been seen with losartan.[2] [3]

A unique feature of ACE inhibitors is that their vasodilator effect is not accompanied by reflex cardioacceleration[19] [20] or an increase in plasma norepinephrine as an index of an increase in sympathetic tone.[21] [22] In the present study, no significant increase in heart rate in response to either the 25- or 100-mg dose of the AT_1 receptor antagonist was observed. However, unlike observations with ACE inhibitors, plasma norepinephrine moderately increased in response to the 100-mg dose. Further studies are needed to confirm this unexpected finding and, if present, to explore whether it indeed reflects baroreflex-mediated increased sympathetic nerve activity or whether it is a result of a decreased clearance of norepinephrine.

In contrast to observations with losartan,[23] repeated administration of irbesartan was not associated with a decrease in the serum uric acid concentration nor did it have an uricosuric effect, confirming studies in healthy volunteers.[24] This difference between losartan and the tested compound suggests that the effects of losartan on uric acid are drug specific and not linked to AT_1 receptor blockade. This view is supported by studies showing that the uricosuric effect of losartan is unrelated to the state of activation of the renin-angiotensin system.[25]

Endogenous creatinine clearance as an estimate of glomerular filtration rate did not change in response to repeated administration of irbesartan. This finding agrees with experimental and clinical studies with losartan[25] and ACE inhibitors.[26] Since we did not control salt intake in this study, it is impossible to say whether repeated administration of irbesartan has any natriuretic effect. However, the observation that body weight did not change in any of the four treatment groups suggests that this effect, if present at all, is small.

In this study, the maximal dose of the AT_1 receptor antagonist tested was 100 mg. With this dose, average 24-hour ambulatory BP compared with placebo decreased by 12.1 mm Hg systolic and 7.2 mm Hg diastolic. The important question of whether a higher dose produces a greater antihypertensive effect cannot be answered at this moment and requires further investigation. Also, further studies are required to evaluate how the antihypertensive effect of irbesartan compares with that of ACE inhibitors. Although data are still preliminary, studies with losartan seem to indicate that with this new class of compounds an antihypertensive response can be obtained that is similar to that obtained with ACE inhibitors.[27]

In conclusion, this study shows that repeated oral administration of the AT_1 receptor antagonist irbesartan lowers BP in patients with mild to moderate hypertension on a normal sodium diet. In accordance with experimental studies, the renin dependency of BP appears to be an important determinant of the antihypertensive effect of the compound; therefore, it is expected that the BP-lowering effect can be potentiated by reducing salt intake or by inducing salt depletion with concomitant administration of a diuretic. Finally, unlike observations with losartan, irbesartan did not lower serum uric acid, suggesting that this effect of losartan is unrelated to AT_1 receptor blockade.

Footnotes

Reprint requests to Dr A.H. van den Meiracker, Department of Internal Medicine I, University Hospital Dijkzigt, Room L253, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.

Received May 23, 1994; accepted September 8, 1994.

References

1. Nelson E, Merrill D, Sweet C, Badstreet D, Panebianco D, Byny R, Herman T, Lasseter K, Levy B, Lewis G, et al. Efficacy and safety of oral MK-954 (Dup 753), an angiotensin II receptor antagonist in essential hypertension. *J Hypertens*. 1991;9 (suppl 6):s468-s469. Abstract.
2. Christen Y, Waeber B, Nussberger J, Porchet M, Borland RM, Lee RJ, Maggon K, Shum L, Timmermans PBMWM. Oral administration of Dup 753, a specific angiotensin II receptor antagonist, to normal male volunteers: inhibition of the response to exogenous angiotensin I and II. *Circulation.* 1991;83:1333-1342. [Abstract/Free Full Text]
3. Goldberg MR, Tanaka W, Barchowsky A, Bradstreet TE, McCrea J, Lo MW, McWilliams EJ Jr, Bjornsson TD. Effects of losartan on blood

pressure, plasma renin activity, and angiotensin II in volunteers. *Hypertension.* 1993;21:704-713. [Abstract]

4. Tsunoda K, Abe K, Hagino T, Omat K, Misawa S, Imai Y, Yoshinaga K. Hypotensive effect of losartan, a non-peptide angiotensin II receptor antagonist, in essential hypertension. *Am J Hypertens.* 1993;6:28-32. [Medline] [Order article via Infotrieve]
5. Wexler RR, Carin DJ, Duncia JV, Johnson AL, Wells GJ, Chiu AT, Wong PC, Timmermans PBMWM. Rationale for the chemical development of angiotensin II receptor antagonists. *Am J Hypertens.* 1992;5:209S-220S. [Medline] [Order article via Infotrieve]
6. Cazaubon C, Gougat J, Bousquet F, Guiraudou P, Gayraud R, Lacour C, Roccon A, Galindo G, Barthelemy G, Gautret B, et al. Pharmacological characterization of SR 47436, a new nonpeptide AT1 subtype angiotensin II receptor antagonist. *J Pharmacol Exp Ther.* 1993;265:826-834. [Abstract/Free Full Text]
7. Sissmann J, Bouroudian M, Armagnac C, Donazollo Y, Latreille M, Panis R. Angiotensin II blockade in healthy volunteers: tolerability and impact on renin angiotensin system components of single and repeated doses of a new angiotensin II receptor antagonist SR 47436 (BMS 186295). *J Hypertens.* 1994;12(suppl 3):508. Abstract.
8. Derkx FHM, Tan-Tjiong H, Wenting GJ, Boomsma F, Schalekamp MADH. Asynchronous changes in prorenin and renin secretion after captopril in patients with renal artery stenosis. *Hypertension.* 1983;5:244-256. [Abstract]
9. Admiraal PJJ, Derkx FHM, Danser AHJ, Pieterman H, Schalekamp MADH. Metabolism and production of angiotensin I in different vascular beds in subjects with hypertension. *Hypertension.* 1990;15:44-55. [Abstract]
10. Véniant M, Clozel JP, Hess P, Fischli W. Effects of renin-angiotensin system blockade in guinea pigs. *Hypertension.* 1992;19:225-262.
11. van der Hoorn FAJ, Boomsma F, Man in `t Veld AJ, Schalekamp MADH. Determination of catecholamines in human plasma by high performance liquid chromatography: comparison between a new method with fluorescence detection and an established method with electrochemical detection. *J Chromatogr.* 1989;487:17-27. [Medline] [Order article via Infotrieve]
12. Keeton TK, Campbell WB. The pharmacologic alteration of renin release. *Pharmacol Rev.* 1981;31:81-227.
13. Johns DW, Peach MJ, Gomez RA, Inagami T, Carey RM. Angiotensin II regulates renin gene expression. *Am J Physiol.* 1990;259:F882-F887. [Abstract/Free Full Text]
14. Wong PC, Price WA, Chiu AT, Duncia JV, Carini DJ, Wexler RR, Timmermans PBMWM. Hypotensive action of DuP 753, an angiotensin II antagonist, in spontaneously hypertensive rats. *Hypertension.* 1990;15:459-468. [Abstract]
15. Wong PC, Price WA, Chiu AT, Duncia JV, Carini DJ, Wexler RR, Timmermans PBMWM. Non-peptide angiotensin II receptor antagonists: antihypertensive activity of Dup 753, an orally active antihypertensive agent. *J Pharmacol Exp Ther.* 1990;252:726-732. [Abstract/Free Full Text]
16. Abdelrahman AM, Burrell LM, Johnston CI. Blockade of the renin-angiotensin system at different sites: effect on renin, angiotensin and aldosterone. *J Hypertens.* 1993;11(suppl 3):S23-S26.
17. Wong PC, Price WA, Chiu AT, Carini DJ, Duncia JV, Johnson AL, Wexler RR, Timmermans PBMWM. Non-peptide angiotensin II receptor antagonists: studies with EXP9270 and DuP 753. *Hypertension.* 1990;15:823-834. [Abstract]
18. Tofovi S, Pang A, Jackson EK. Effects of angiotensin subtype 1 and subtype 2 receptor antagonists in normotensive versus hypertensive rats. *Hypertension.* 1991;18:774-782. [Abstract]
19. Gavras H, Brunner HR, Turini GA, Kershaw GR, Tufft CP, Cuttelod S, Gavras I, Vukovich RA, McKinstry DN. Antihypertensive effect of oral angiotensin converting enzyme inhibitor SQ 14225 in man. *N Engl J Med.* 1978;298:991-995. [Abstract]
20. Mancia G, Parati G, Pomidossi G, Grassi G, Bertinieri G, Buccino N, Ferrari A, Gregorini L, Rupoli L, Zanchetti A. Modification of arterial baroreflexes by captopril in essential hypertension. *Am J Cardiol.* 1982;49:1415-1419. [Medline] [Order article via Infotrieve]

21. Bravo EL, Tarazi RC. Converting enzyme inhibition with an orally active compound in hypertensive man. *Hypertension.* 1979;1:39-46. [Abstract]
22. Nicholls MG, Espiner EA, Miles KD, Zweifler AJ, Julius S. Evidence against an interaction of angiotensin II with the sympathetic nervous system in man. *Clin Endocrinol.* 1981;15:423-430. [Medline] [Order article via Infotrieve]
23. Nakashima M, Uematsu T, Kosuge K, Kanamaru M. Pilot study of the uricosuric effect of Dup 753, a new angiotensin II receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol.* 1992;42:333-335. [Medline] [Order article via Infotrieve]
24. Burnier M, Hagmann M, Declacretaz E, Brouard R, Armagnac C, Nussberger J, Waeber B, Brunner HR. The angiotensin II antagonist SR 47436 (BMS 186295) increases dose-dependently urinary sodium excretion but not uric acid in healthy normotensive volunteers. *J Hypertens*. 1994;12 (suppl 3):s98. Abstract.
25. Burnier M, Rutschmann B, Nussberger J, Versaggi J, Shahinfar S, Waeber B, Brunner HR. Salt-dependent renal effects of an angiotensin II antagonist in healthy subjects. *Hypertension.* 1993;22:339-347. [Abstract]
26. Hollenberg NK, Meggs LG, Williams GH, Katz J, Garnic JD, Harrington DP. Sodium intake and renal responses to captopril in normal man and in essential hypertension. *Kidney Int.* 1981;20:240-245. [Medline] [Order article via Infotrieve]
27. Weber A. Clinical experience with the angiotensin II receptor antagonist losartan: a preliminary report. *Am J Hypertens*. 1992;5(suppl):247S-251S.

This article has been cited by other articles: (Search Google Scholar for Other Citing Articles)

European Respiratory Journal HOME

S. Andreas, C. Herrmann-Lingen, T. Raupach, L. Luthje, J. A. Fabricius, N. Hruska, W. Korber, B. Buchner, C-P. Criee, G. Hasenfuss, and P. Calverley
Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial
Eur. Respir. J., May 1, 2006; 27(5): 972 - 979.
[Abstract] [Full Text] [PDF]

Circulation HOME

F. G. Spinale, R. Mukherjee, J. P. Iannini, S. Whitebread, L. Hebbar, M. J. Clair, D. M. Melton, M. H. Cox, P. B. Thomas, and P. B. Marc de Gasparo
Modulation of the Renin-Angiotensin Pathway Through Enzyme Inhibition and Specific Receptor Blockade in Pacing-Induced Heart Failure : II. Effects on Myocyte Contractile Processes
Circulation, October 7, 1997; 96(7): 2397 - 2406.
[Abstract] [Full Text]

Hypertension HOME

S. K. Gandhi, D. H. Ryder, and N. J. Brown
Losartan Blocks Aldosterone and Renal Vascular Responses to Angiotensin II in Humans
Hypertension, December 1, 1996; 28(6): 961 - 966.
[Abstract] [Full Text]

HYPERTENSION