Original Article

A Randomized Trial of the Effect of an Angiotensin II Receptor Blocker SR47436 (Irbesartan) on 24-Hour Blood Pressure in Patients with Essential Hypertension

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The aim of this placebo-controlled, double-blind randomized study was to evaluate the duration of the effect of once-daily administration of irbesartan in patients with essential hypertension. After a placebo run-in baseline period (of 2–4 weeks), 79 patients were randomized to either irbesartan (one 100 mg tablet per day) or placebo, for 6 weeks. The primary outcome was the reduction in the mean 24-h blood pressure (BP) as assessed by ambulatory BP monitoring under standardized conditions. Seventy-six patients completed the study protocol. In the irbesartan group, the average reductions in 24-h systolic and diastolic BPs were 5.8 and 3.4 mmHg, respectively (95% confidence interval: 3.2–8.4/1.6–5.1 mmHg), and in the placebo group, they were −1.7 and −0.5 mmHg, respectively (95% confidence interval: −4.3 to 1.0/−1.8 to 0.7 mmHg). There were statistically significant differences in the average reductions of 24-h BP (7.5/3.9 mmHg, $p<0.001$), daytime BP (8.6/4.0 mmHg, $p<0.001$) and nighttime BP (6.1/3.4 mmHg, $p<0.05$) as well as casual BP (9.0/5.0 mmHg, $p<0.001$). The trough/peak (T/P) ratios for the systolic and diastolic BPs were 0.84 and 0.78, respectively, in the irbesartan group. The incidence of adverse events was similar in both groups. The results showed that irbesartan administered 100 mg once daily was well tolerated in the treatment of essential hypertension and was effective in producing sustained 24-h BP control. (*Hypertens Res* 2008; 31: 1753–1763)

Key Words: SR47436, irbesartan, double-blind randomized study, ambulatory blood pressure monitoring, essential hypertension

Introduction

Hypertension is a major risk factor for cardiovascular diseases (*1*). The aim of antihypertensive therapy is to lower the morbidity and mortality from cardiovascular diseases, and a number of intervention studies have shown that such therapy is effective (*2*). Given the long-term objectives of antihypertensive treatment aimed at cardiovascular disease prevention, it is desirable to use an antihypertensive agent which reliably controls blood pressure (BP) with few adverse drug reactions when administered once daily.

Blood pressure can now be measured non-invasively for 24 consecutive hours (*3–5*). Several studies have shown that the average BP measured by ambulatory BP monitoring (ABPM) correlates more strongly with the severity of hypertensive organ damage than the values measured during outpatient visits (*6*). In addition, the guidelines for clinical assessment of antihypertensive drugs in Japan recommend the use of trough/peak (*T/P*) ratios based on ABPM measurements to investigate the duration of therapeutic effects (*7*).

SR47436 (irbesartan) is a non-peptide angiotensin II (AII) receptor blocker that can be administered orally. Irbesartan selectively binds to a type 1 AII receptor and lowers BP by
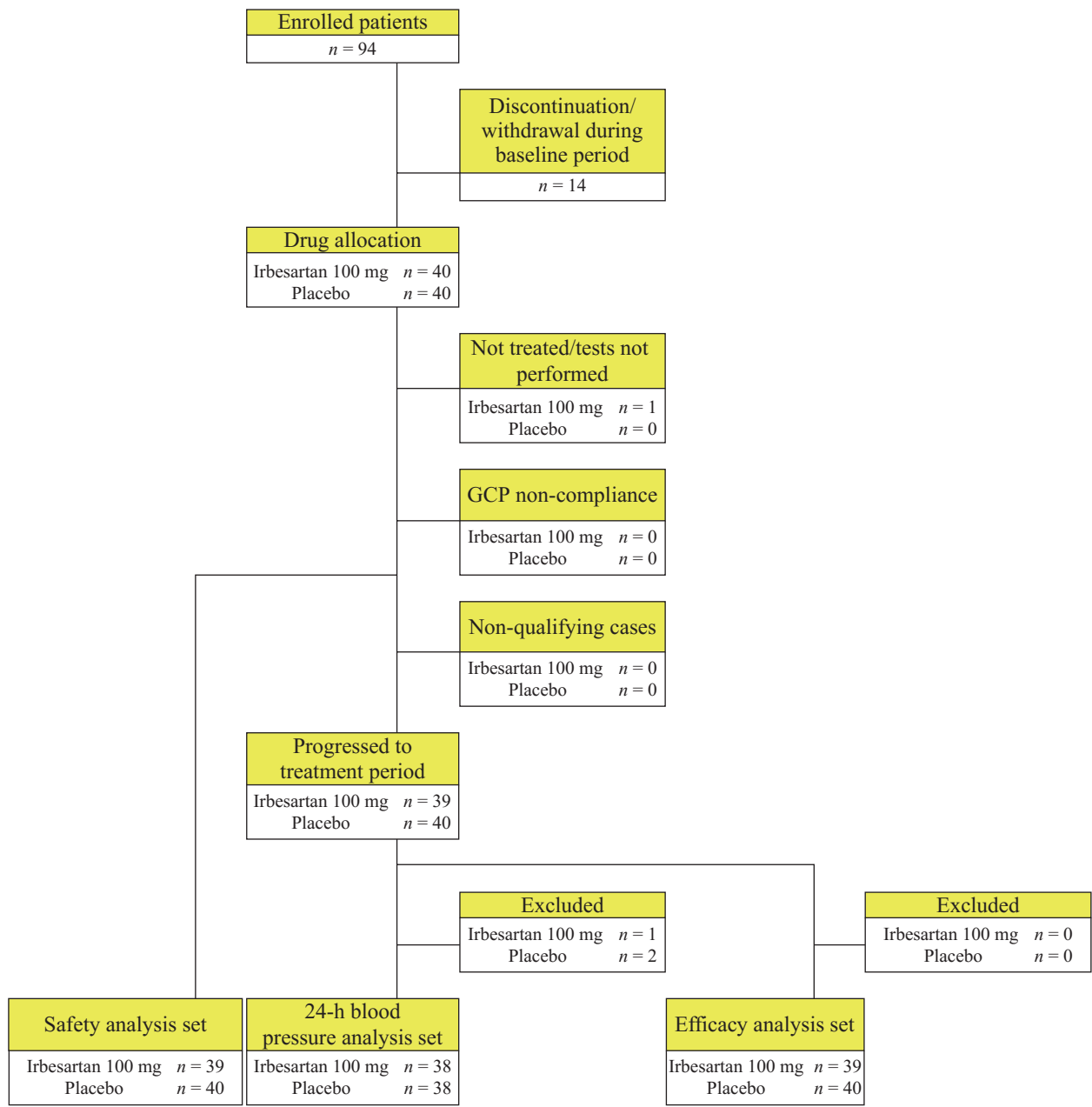
Fig. 1. *Flowchart depicting the inclusion and exclusion of study subjects.*

competing with AII to bind to the receptor. In Japan, single-dose and repeated-dose studies have been conducted among healthy male volunteers. Among those with mild to moderate essential hypertension, two studies of irbesartan have been conducted: a pilot study and a late phase II clinical study (*8*). The results of these studies showed that irbesartan could safely and effectively lower BP when administered once daily, and the optimal clinical doses were estimated at 50–100 mg/d.

The present study investigated the duration of the anti-hypertensive effect of irbesartan using ABPM. The effect of once-daily administration of 100 mg of irbesartan was evaluated in a placebo-controlled, double-blind randomized study.

Methods

The present study was conducted according to the "Good Clinical Practice for Trials on Drugs (GCP)" ordinance of Japan (Pharmaceutical Affairs Law, Article 14, Section 3 and Article 80, Sections 2-1, 4 and 5) established in accordance with the Declaration of Helsinki. The study was also approved by the institutional review board of each participat-
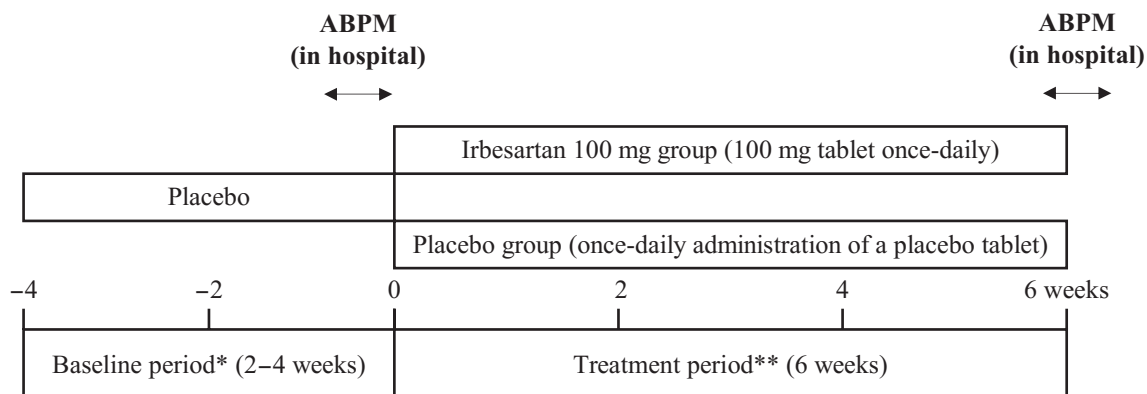
Fig. 2. *Study timeline. *Lengthened by up to 2 weeks depending on patient circumstances. **Shortened or lengthened by 1 week depending on patient circumstances.*

ing medical institution.

Subjects

Eligible subjects were patients with essential hypertension who visited one of the ten medical institutions listed in the Appendix between August 2001 and June 2002. Prior to the start of the baseline period, the investigators used a GCP-compliant consent form to explain the details of the present study to the subjects, and informed consent was obtained in writing from all subjects.

Inclusion criteria at the start of the recruitment were as follows: 1) age from 25 to 79 years, 2) men or postmenopausal women, 3) outpatients with essential hypertension, 4) untreated with antihypertensive agents or, if treated, willing to forgo current medication during the 4-week placebo run-in baseline period and the 6-week main study period. Inclusion criteria at the start of the study period were as follows: 1) stable sitting BP in the last two measurements during the baseline period, 2) sitting systolic BP of 150 mmHg or above and diastolic BP of 95 mmHg or above, or systolic BP of 160 mmHg or above and diastolic BP of 90 mmHg or above, 3) sitting diastolic BP of less than 120 mmHg, 4) mean 24-h systolic BP of 130 mmHg or above, or diastolic BP of 80 mmHg or above. The reason we used several criteria for casual BP was that we wanted to include only patients with definite systolic-diastolic hypertension. Patients with secondary or malignant hypertension, cardiovascular diseases such as stroke, myocardial infarction and heart failure, renal failure or liver dysfunction, and patients judged unsuitable for participation by the investigator were excluded from the present study.

A total of 94 subjects were enrolled in the present study (Fig. 1). Of these patients, 14 discontinued or withdrew during the baseline period. Hence, drug allocation was performed in 80 patients (irbesartan group: $n=40$; placebo group: $n=40$). One patient in the irbesartan group was excluded from the study because the proper allocated drug was not adminis-

tered. Consequently, 79 patients (irbesartan group: $n=39$; placebo group: $n=40$) progressed to the treatment period, and their data were used for the evaluation of safety and efficacy. During the treatment period, GCP compliance guidelines were upheld for all 79 patients. Ambulatory BP monitoring was not properly performed in three patients (irbesartan group: $n=1$; placebo group: $n=2$); therefore, for the analysis of 24-h BP, we used data from the remaining 76 patients (irbesartan group: $n=38$; placebo group: $n=38$).

Based on the findings of another ABPM study of irbesartan (*9*), it was estimated that the mean difference in the reduction in mean 24-h BP between the irbesartan group and placebo group would be 5.0 mmHg with a SD of 6.0 mmHg. Using these values, the required number of subjects to detect a difference between the two groups was estimated to be 23 per group (power of test: 80%, $\alpha=0.05$, two-sided). Therefore, the target number of cases was set at 30 subjects per group (total number of subjects: 60), allowing for dropouts and withdrawals.

Investigational Drugs

Irbesartan (100 mg) tablets and placebo tablets, indistinguishable in appearance, were used. The tablets were randomly distributed within each of the 30 blocks used; each block consisted of four patients (two in the irbesartan group and two in the placebo group).

Administration of the Drugs

During the baseline run-in period, one placebo tablet was administered once daily after breakfast for 2 weeks to patients with untreated essential hypertension and for 4 weeks to patients who stopped antihypertensive therapy before enrolling (Fig. 2). During the treatment period, one tablet (either 100 mg of irbesartan or placebo) was administered once daily after breakfast for 6 weeks.

Table 1. Characteristics of the Study Population

Item	Irbesartan 100 mg group	Placebo group	Total
Total number of subjects	38 (100.0)	38 (100.0)	76 (100.0)
Gender			
Male	28 (73.7)	25 (65.8)	53 (69.7)
Female	10 (26.3)	13 (34.2)	23 (30.3)
Age (years)	58.9±8.3	58.8±9.4	58.9±8.8
Body weight (kg)	66.5±13.4	64.6±10.9	65.5±12.2
Height (cm)	162.1±7.6	161.0±8.3	161.5±7.9
Complications			
No	9 (23.7)	7 (18.4)	16 (21.1)
Yes	29 (76.3)	31 (81.6)	60 (78.9)
WHO-ISH 1993 Guidelines			
Stage I	13 (34.2)	15 (39.5)	28 (36.8)
Stage II	25 (65.8)	22 (57.9)	47 (61.8)
Stage III	0 (0.0)	1 (2.6)	1 (1.3)
History of antihypertensive therapy			
No past history	8 (21.1)	11 (28.9)	19 (25.0)
Drug taken in the past	9 (23.7)	9 (23.7)	18 (23.7)
Drug taken until just before the study	21 (55.3)	18 (47.4)	39 (51.3)

Data are mean±SD or *n* (%).

Table 2. Distribution of Baseline Values

Item	Irbesartan 100 mg group (*n*=38)	Placebo group (*n*=38)	Total (*n*=76)
Mean 24-h BP during baseline period (mmHg)			
Systolic BP	145.0±10.9	142.9±10.6	143.9±10.7
Diastolic BP	95.0±8.8	92.0±7.8	93.5±8.4
Casual BP during baseline period (mmHg)			
Systolic BP	163.4±11.3	163.7±9.1	163.6±10.2
Diastolic BP	100.0±5.4	99.2±5.7	99.6±5.5
Casual pulse rate during baseline period (beats/min)	73.2±13.1	72.2±11.4	72.7±12.2

Data are mean±SD. BP, blood pressure.

Use of other antihypertensive drugs was prohibited during the baseline and treatment periods. Use of the following drugs was also prohibited unless necessary: psychotropic agents, anti-anxiety drugs, sedatives, hypnotic agents, analgesics, central acting muscle relaxants, phenothiazine antihistamines, or phosphodiesterase-5 inhibitors.

Measurements

Casual BP and pulse rate were measured at 2-week intervals in a sitting position after sufficient rest. A tablet of irbesartan or placebo was taken before the measurement. Casual BP was measured twice, and the average values were used for analysis. At the end of the baseline period and at the end of the treatment period, casual BP was also measured in the supine, and standing positions.

At the end of the baseline period and at the end of the treat-ment period, ABPM was carried out for 26 consecutive hours in the hospital using a portable automatic sphygmomanome-ter (TM-2421; A&D Co., Ltd., Tokyo, Japan) at 15-min inter-vals during the day (6:00–21:00) and at 30-min intervals at night (21:00–6:00). The same sphygmomanometer was used for each patient. During ABPM, the investigational drug was administered at 10 AM. The patients were instructed to relax the upper arm as a cuff was fastened in place and to remain in a sitting position while BP was monitored at peak (3–6 h after administration) and trough (23–24 h after administration) hours. The patients were also instructed to record daily activ-ities, such as the times of meals, sleeping and getting up.

At the end of the baseline period and at the end of the treat-ment period (or at discontinuation of treatment), the follow-ing tests were conducted: hematology, blood chemistry, urinalysis, chest X-ray, electrocardiography, and funduscopy (if possible).
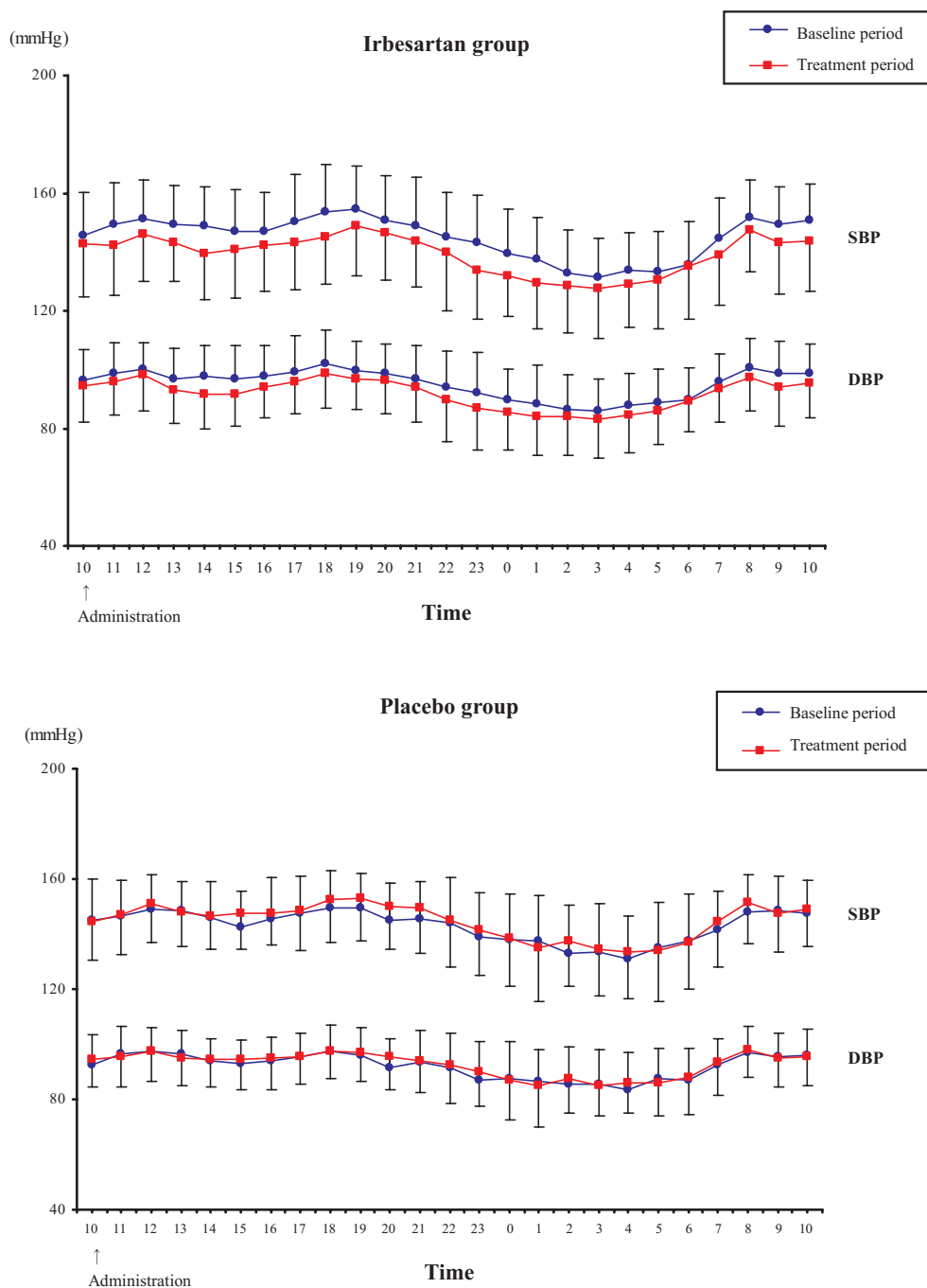
Fig. 3. *Twenty-four-hour blood pressure in the irbesartan and placebo groups. Mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

Adverse Events

All subjective symptoms and objective findings or diseases which newly appeared or which were exacerbated during the study were noted and the details were recorded. Any abnormal changes in laboratory data were evaluated based on a comparison of observed values in the baseline and treatment periods. If possible, follow-up investigations were performed until recovery.

Overall Safety

To investigate the severity of adverse drug reactions, overall safety of use was rated on a scale of 1–5: 1, safe (no safety
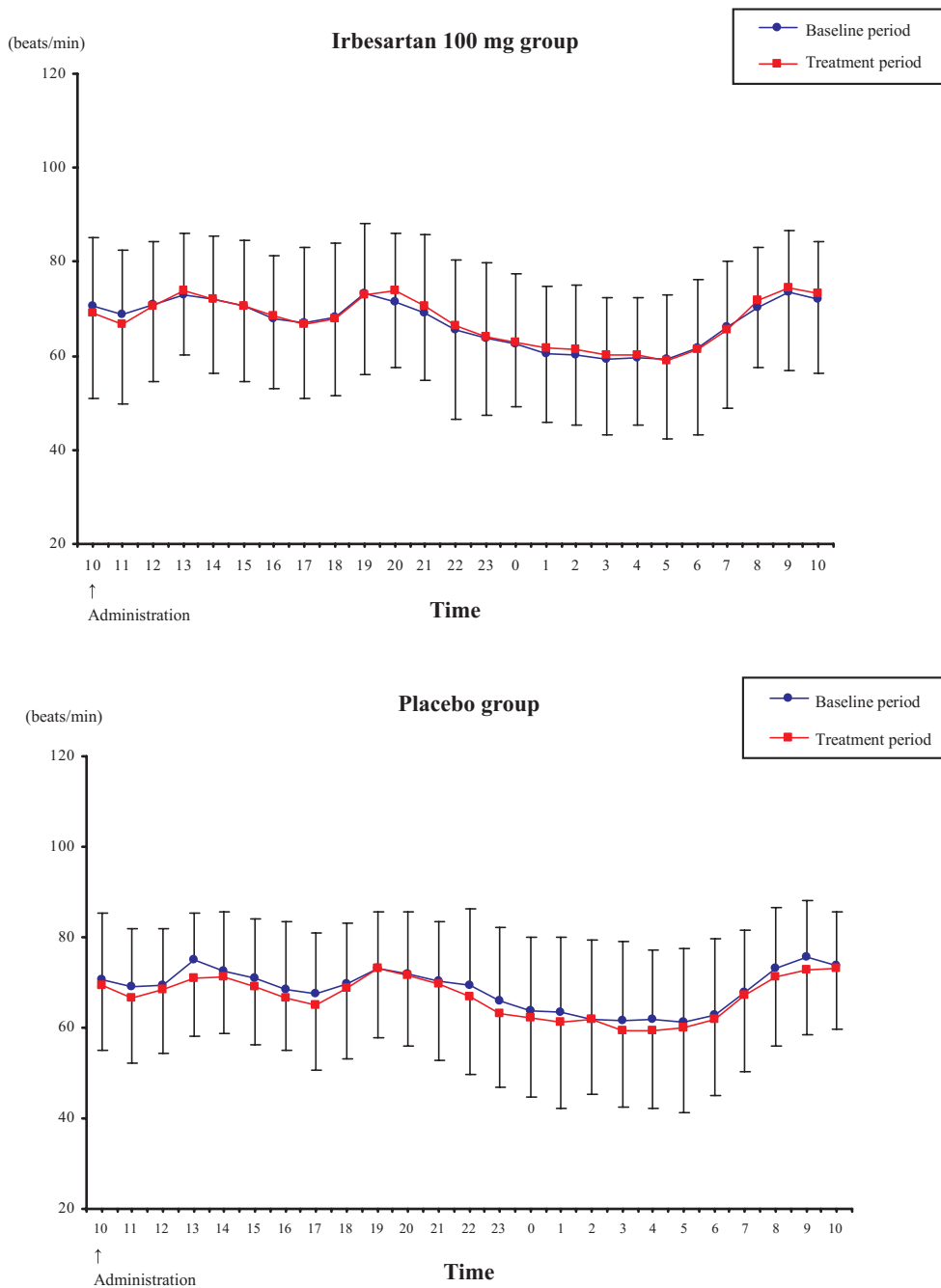
Fig. 4. *Twenty-four-hour pulse rate in the irbesartan and placebo groups. Mean±SD.*

problems, *i.e.*, no adverse effects occurred); 2, slightly unsafe (mild adverse reaction occurred but no special treatment was needed and treatment was continued); 3, probably unsafe (dosage reduction or other measures were required); 4, unsafe (treatment with the investigational drug was, or should have been, discontinued); 5, no information available. In the event that treatment was discontinued for some reason, the investigator also evaluated the overall safety of use on the same scale. Patients for whom an evaluation could not be made for

some reason were classified as "no information available."

Analysis

The primary objective was to compare the efficacy of 100 mg irbesartan compared with placebo group on reducing the mean 24-h BP from ABPM data. The statistical analysis was conducted using SAS version 6.12 (SAS Japan Inc., Tokyo, Japan). The differences between groups were evaluated by

Table 3. Reductions in 24-h, Daytime and Nighttime BP

Item and time period	Group	n	Baseline period mean	Treatment period mean	Reduction		Difference between treatment groups		
					Mean	95% confidence interval	p*	Mean	95% confidence interval
Systolic BP									
24 h	Irbesartan	38	145.0	139.2	5.8	3.2–8.4	0.0001	7.5	3.8–11.1
	Placebo	38	142.9	144.6	−1.7	−4.3–1.0			
Daytime (11:00–21:00)	Irbesartan	38	150.1	143.8	6.3	3.2–9.5	0.0001	8.6	4.4–12.8
	Placebo	38	146.9	149.1	−2.3	−5.1–0.6			
Nighttime (0:00–5:00)	Irbesartan	38	134.8	129.5	5.3	2.3–8.3	0.0100	6.1	1.5–10.7
	Placebo	38	134.8	135.6	−0.8	−4.4–2.7			
Diastolic BP									
24 h	Irbesartan	38	95.0	91.7	3.4	1.6–5.1	0.0004	3.9	1.8–6.0
	Placebo	38	92.0	92.5	−0.5	−1.8–0.7			
Daytime (11:00–21:00)	Irbesartan	38	98.6	95.2	3.4	1.3–5.4	0.0018	3.9	1.5–6.4
	Placebo	38	95.0	95.6	−0.6	−2.0–0.8			
Nighttime (0:00–5:00)	Irbesartan	38	87.7	84.4	3.3	1.2–5.4	0.0218	3.4	0.5–6.2
	Placebo	38	86.0	86.1	−0.1	−2.1–2.0			

Unit: mmHg. BP, blood pressure. *t-test.

Table 4. *T/P* ratios as Determined by ABPM

Item	Group	T value (mmHg)	P value (mmHg)	T/P ratio	Placebo-corrected		
					T value (mmHg)	P value (mmHg)	T/P ratio
Systolic BP	Irbesartan 100 mg	6.6	7.8	0.84	6.9	9.0	0.77
	Placebo	−0.3	0.1				
Diastolic BP	Irbesartan 100 mg	4.3	5.4	0.78	3.7	5.8	0.64
	Placebo	0.5	0.5				

T, trough; *P*, peak; ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

the *t*-test. The secondary objectives were to assess some other measures of antihypertensive effects and the overall safety of use. The overall safety of use was assessed in an exploratory manner by tabulating the incidence, calculating descriptive statistics, and preparing tables and figures. All tests were two-sided and conducted at the 5% level of significance, unless otherwise specified.

Values are expressed as mean±SD and 95% confidence intervals were used. The Clopper-Pearson method was used to estimate the confidence interval of ratios.

Results

Baseline Characteristics

The patient characteristics, baseline values of BPs and pulse rate are shown in Tables 1 and 2. There were no significant differences between the irbesartan and placebo groups. The mean 24-h BP during the baseline period in the irbesartan group were 145.0±10.9 mmHg systolic and 95.0±8.8 mmHg diastolic and 142.9±10.6 mmHg systolic and 92.0±7.8 mmHg diastolic in the placebo group.

Changes in BP and Pulse Rate during ABPM

Systolic and diastolic BPs and pulse rate, as measured by ABPM, are shown in Figs. 3 and 4. At all measurement points, systolic and diastolic BPs during the treatment period in the irbesartan group were lower than those during the baseline period. In contrast, no marked differences in systolic and diastolic BPs were noted between the baseline and treatment periods for the placebo group. For pulse rate, no marked changes were observed between the baseline and treatment periods for either the irbesartan or the placebo group (Fig. 4).

In the irbesartan group, 24-h systolic and diastolic BPs were significantly reduced whereas the values in the placebo group were unchanged (Table 3). The differences between the groups in the mean reduction in BP were 7.5/3.9 mmHg in 24

h, 8.6/4.0 mmHg in daytime, and 6.1/3.4 mmHg in nighttime.

The reductions in trough systolic and diastolic BPs were 6.6 and 4.3 mmHg, respectively, in the irbesartan group and −0.3 and 0.5 mmHg, respectively, in the placebo group (Table 4). The differences in the reductions for both the trough systolic and diastolic BPs were statistically significant. Trough and peak values were calculated from the mean reduction in BP during 24 h. The *T/P* ratios for systolic and diastolic BPs in the irbesartan group were 0.84 and 0.78, respectively (Table 4). Placebo-corrected *T/P* ratios were also calculated by taking the mean reduction in trough and peak BPs and correcting it for the mean reduction in the placebo group. The placebo-corrected *T/P* ratios for systolic and diastolic BPs were 0.77 and 0.64, respectively.

Changes in Casual BP and Pulse Rate

Changes in outpatient readings for sitting BP and pulse rate are shown in Fig. 5. In the irbesartan group, both systolic and diastolic BPs were significantly decreased at the second week (by 9.1 and 6.0 mmHg, respectively) of the treatment period, and remained significantly low up to the sixth week. In the placebo group, small but significant reductions in BPs were observed from the fourth week of the treatment. No marked changes in pulse rate were observed in either group.

Casual BP values during the baseline period and at the end of the treatment period as well as the reduction in BP are shown in Table 5. Systolic and diastolic BPs were significantly reduced in the irbesartan group and the difference between the groups was 9.0 mmHg systolic and 5.0 mmHg diastolic.

Adverse Events

Of the 79 patients (irbesartan group: $n=39$, placebo group: $n=40$), 20 (51.3%) patients in the irbesartan group experienced a total of 30 adverse events. The main adverse events included common cold syndrome (6 events), headache (2), diarrhea (2), rhinitis (2), and contusion (2). Of these, 2 (5.1%) patients reported adverse drug reactions: thirst (1) and gastric discomfort (1). In the placebo group, 20 (50.0%) patients experienced a total of 33 adverse events. The main adverse events included common cold syndrome (4 events), palpitation (3), insomnia (3), and headache (3). Of these, 5 (12.5%) patients reported adverse drug reactions: cerebral hemorrhage (1), cough (1), headache (1), palpitation (1), and anastomotic ulcer (1).

In the irbesartan group, eight abnormal changes in clinical laboratory findings were reported in six (15.4%) patients including increased creatine kinase (4 events). Of these, 2 (5.1%) displayed 3 adverse drug reactions: increased creatine kinase (1), microscopic hematuria (1), and increased urine WBC (1). In the placebo group, 11 (27.5%) patients experienced a total of 14 abnormal changes in clinical laboratory findings including increased serum uric acid (3 events) and
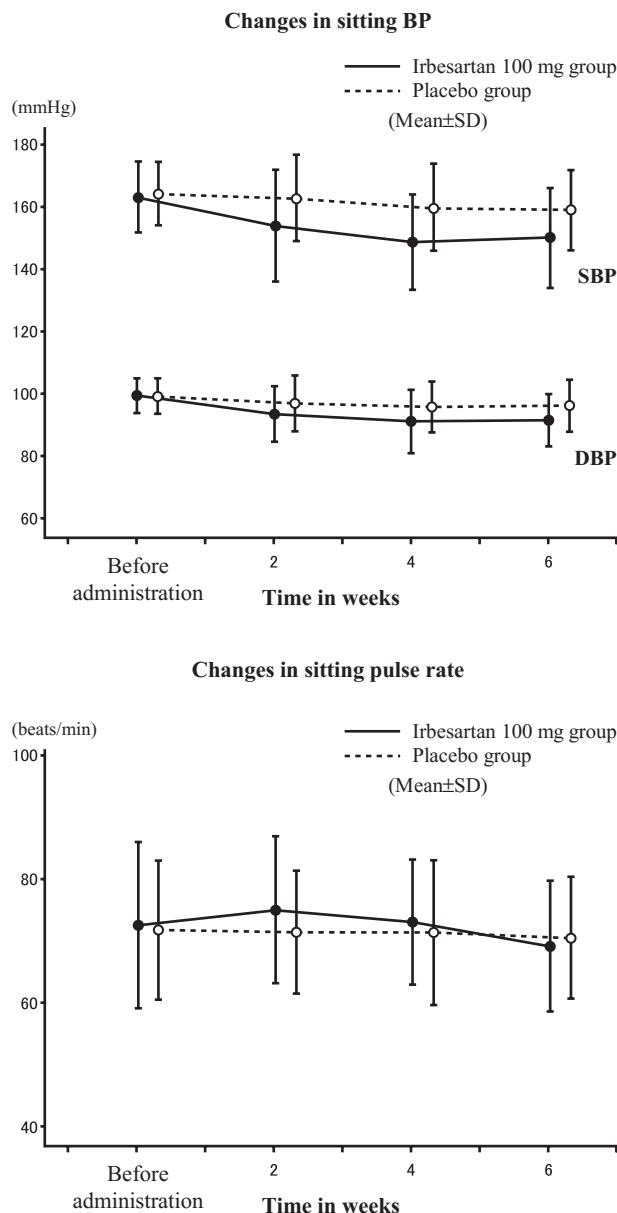

Changes in sitting BP

Changes in sitting pulse rate

Fig. 5. *Changes in sitting blood pressure and pulse rate measured during outpatient visits. Mean ±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

increased serum bilirubin (2). Of these, 4 (10.0%) patients displayed adverse drug reactions: increased serum uric acid (2), increased serum cholesterol (1), and increased serum bilirubin (1).

Overall Safety

The results of the overall safety evaluation are shown in Table 6. The safety rates (defined as the percentage of patients in whom the investigational drug was regarded as "safe") in the irbesartan and placebo groups were 92.3% (36/39) and 80.0%

Table 5. Reduction in Casual Blood Pressure

Item	Group	n	Baseline period mean	Treatment period mean	Reduction		Differences between treatment groups		
					Mean	95% confidence interval	p*	Mean	95% confidence interval
Systolic BP	Irbesartan 100 mg	39	163.5	150.4	13.1	9.8–16.3	0.0001	9.0	4.7–13.4
	Placebo	39	164.2	160.1	4.1	1.1–7.0			
Diastolic BP	Irbesartan 100 mg	39	99.7	92.0	7.7	5.7–9.8	0.0004	5.0	2.3–7.7
	Placebo	39	99.3	96.6	2.7	0.9–4.5			

Unit: mmHg. BP, blood pressure. *t-test.

Table 6. Overall Safety Rating

Group	Safe	Slightly unsafe	Probably unsafe	Unsafe	No information available	Total	Safety rate (%)	95% confidence interval (%)
Irbesartan 100 mg	36	2	1	0	0	39	92.3	79.1–98.4
Placebo	32	5	2	1	0	40	80.0	64.4–90.9

(32/40), respectively. Hence, a similarly high level of safety was observed in both groups.

Discussion

The present study demonstrates that once-daily administration of 100 mg of irbesartan decreases the BP of patients with essential hypertension for up to 24 h. With ABPM, BP data can be obtained outside the examination room and the white coat effect can be eliminated. The placebo effect was also considered to be nonexistent or minimal in these ABPM studies (*10*). Given that ABPM can measure BP at both peak and trough blood levels, it has become a popular choice for investigating the duration of drug effects. The current "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH) guideline proposes that the T/P ratio be evaluated using ABPM and that the placebo-subtracted T/P ratio be at least 50% (*7*). Despite the usefulness of ABPM, no placebo-controlled clinical studies have been conducted in Japan among hypertensive patients. The present study was a placebo-controlled, double-blind randomized trial, and ABPM was carried out under standardized conditions. These methodological conditions strengthen the scientific value of the findings.

The present study showed that irbesartan significantly reduced 24-h, daytime, and nighttime BPs whereas no significant changes in these readings were observed for the placebo. These results thus confirm that irbesartan has a stable antihypertensive effect over 24 h, and that the placebo effect is negligible. In the present study, the ABPM was performed in the hospital so that the monitoring conditions were identical during the baseline and treatment periods, BP was monitored at short intervals, and the mean values at each hour were cal-

culated at 1-h intervals to minimize the effects of measurement error. Thus, a high level of accuracy was achieved because the mean values for 24-h BP readings were calculated under these strict conditions. The T/P ratios for systolic and diastolic BPs in the irbesartan group were 0.84 and 0.78, respectively, and the placebo-corrected T/P ratios were 0.77 and 0.64, respectively. These results suggest that once-daily administration of 100 mg of irbesartan is highly effective for 24 h without altering the diurnal BP profile.

A placebo-controlled ABPM study of irbesartan (*9*) has been conducted in Italy. The results from the Italian study cannot be simply compared with those from the present study because of differences in dose of irbesartan (75 and 150 mg *vs.* 100 mg), treatment period (8 weeks *vs.* 6 weeks) and ABPM condition (outpatient *vs.* inpatient). In the Fogari *et al.* study (*9*), the reduction in 24-h BP following administration of irbesartan 150 mg was 10.5 mmHg for systolic BP and 7.2 mmHg for diastolic BP, with T/P ratios of 0.68 and 0.76, respectively. The reductions in BPs in the Italian study tended to be greater, although the T/P ratio was similar. The smaller reduction in our study may be attributed to the smaller dosage of irbesartan and the in-hospital ABPM, because it is generally recognized that hospitalization reduces BP (*11*). Other possibilities include ethnic differences, and differences in lifestyle, such as dietary sodium intake. It is known that sodium intake, which influences the effect of angiotensin receptor blockers, is generally higher in Japan than in Western countries (*12*). It has also been shown that the antihypertensive effect of inhibititors of the renin angiotensin system is comparable to that of the calcium channel blockers among Caucasians (*13*), but not among the Japanese (*14, 15*).

Angiotensin II receptor blockers (ARBs) are now used widely in the treatment of hypertension because of their BP-

lowering and organ-protective abilities and few side effects. All commercially available ARBs have considerable durations of hypotensive effect and are usually administered once daily. However, the duration of action differs among ARBs mainly due to the different pharmacokinetic properties. The half life of plasma ARBs after oral administration is 1–3 h for losartan, 4–7 h for valsartan, 7–10 h for candesartan, 9–11 h for olmesartan, 11–15 h for irbesartan, and 20–24 h for telmisartan (*16, 17*). A study which compared the effect of irbesartan (150 mg) and valsartan (80 mg) in hypertensive patients showed that irbesartan produced greater reductions in trough BP, morning home BP and the average 24-h BP than valsartan (*18*). In a randomized double-blind trial, the effect of irbesartan (150 mg) on 24-h BP was slightly smaller than olmesartan (20 mg) but was greater than losartan (50 mg) or valsartan (80 mg) (*19*). In a recent systematic review regarding the antihypertensive activity of ARBs, irbesartan ranked second and third among seven ARBs for reductions in 24-h BP and BP during the last 4 h of the interdose period, respectively (*20*). Therefore, among the ARBs, irbesartan is considered to have effective and sustained antihypertensive properties.

In terms of safety, the overall safety rating was even higher for the irbesartan than the placebo. The incidences of adverse events and adverse drug reactions in the irbesartan group were comparable to those in the placebo group. These results confirmed the safety of irbesartan shown in previous studies (*9*).

In summary, a stable antihypertensive effect lasting 24 h was observed following once-daily administration of 100 mg irbesartan. From these findings, we concluded that this regimen can be clinically useful in the treatment of hypertension and that the safety of irbesartan was comparable to that of placebo.

Acknowledgements

Appendix

Medical Institutions and Investigators

Asahikawa City Hospital: Kunihiko Hirasawa, Yasumi Igarashi, Yoshinao Ishii, and Yutaka Yamada; Sapporo Shiraishi Cardiovascular Hospital: Akifumi Kondo, Kimio Soma, Shuzaburo Fukuyama, and Setsuko Kuroda; Ofuna Central Hospital: Takeshi Morishita, Kiyoshi Okamoto, Toshiya Watanabe, Kenichiro Saisho, and Fumihiko Hara; Daishin-kai Ookuma Hospital: Yasushi Wakita, Junichi Nakagawa, and Yasuo Kuroda; National Cardiovascular Center: Yuhei Kawano,* Takeshi Horio, Kei Kamide, and Shin Takiuchi; Osaka Pharmacology Research Clinic: Shigeto Kanada, Junichi Azuma, Toshiro Aoki, Susumu Hashida, Isamu Yamamoto, Saneo Higaki, Yasushi Fujio, Tomohiro Katsuya, Mitsuru Ohishi, Norio Komai, Yoshio Iwashima, Ken Sugimoto, and Masaharu Kaibe; Onomichi General Hospital: Nobuyuki Morishima and Yasuo Ooue; Fukuyo Hospital: Kensuke Fukuoki; National Nagasaki Medical Center: Hironori Ezaki, Hisayuki Hamada, and Hironori Kimura; Keiaikai Nakamura Hospital: Masaharu Hiraga, Hidetaka Akinaga, Takashi Doi, and Yosuke Nakamura (*Study coordinator).

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