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BLOOD PRESSURE MONITORING STUDY OF THE COMPARATIVE ANTIHYPERTENSIVE EFFICACY OF TWO ANGIOTENSIN II RECEPTOR ANTAGONISTS, IRBESARTAN AND VALSARTAN

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ABSTRACT:

Angiotensin II receptor antagonists (AIIRAs) are a recently developed class of antihypertensive agents that have gained widespread use in clinical practice. The first available AIIRA, losartan, subsequent agents of this class including candesartan, irbesartan, and telmisartan, may have greater blood pressure (BP) lowering ability. Little information, however, is available on the comparative antihypertensive efficacy among the newer AIIRAs. The present study addressed this question by comparing two agents for which a greater angiotensin II antagonistic and BP-lowering effect has been demonstrated compared with irbesartan and valsartan. Antihypertensive efficacy in the current analysis was assessed by BP measurements in the physician's office, at home, and by ambulatory monitoring to base results on multiple data collected in different environmental conditions.

Subjects were males and females aged between 18 and 75 years old with mild-to-moderate essential hypertension (defined as seated diastolic blood pressure (DBF) between 95 mmHg and 11OmmHg). Subjects were enrolled from 5 sites in Asser region (Appendix 1).

This randomized, multicenter, double blind, parallel-group study compared the antihypertensive efficacy of irbesartan 150 mg with that of valsartan 80 mg, administered once daily for eight weeks. The primary objective was to compare the change from baseline in diastolic ABP at trough after eight weeks of treatment. Secondary objectives included comparing the changes from baseline in systolic ABP at trough; 24-h mean systolic and diastolic ABP; morning mean and evening mean systolic and diastolic ABP; self-measured DBP and systolic blood pressure (SBP); and office-measured seated DBP and SBP and heart rate at trough. Another secondary objective was to determine the percentage of subjects whose office-measured BP at trough was normalized (DBP<90 mmHg) and who responded to therapy (i.e., whose office-measured DBP was normalized or changed from baseline ≥ 10 mmHg). While both irbesartan and valsartan significantly reduced BP from baseline, in the 303 subjects included in the efficacy analysis for the study's primary objective, irbesartan produced a statistically greater reduction in mean diastolic ABP at trough (-6.73 mmHg vs.-4.84mmHg, respectively; p-0.035). Irbesartan also produced a statistically greater reduction in mean systolic ABP at trough (-11.62 mmHg vs.-7.5 mmHg, respectively; $p < 0.01$). In addition, irbesartan caused a significantly greater reduction compared with valsartan in mean 24-h diastolic and systolic ABP ($p = 0.023$ and $p< 0.01$, respectively); mean daytime diastolic and systolic ABP ($p = 0.017$ and/) - 0.02, respectively); and mean morning self-measured DBP and SBP ($p< 0.01$ for both).

INTRODUCTION

Angiotensin II receptor antagonists (AIIRAs) are a recently developed class of antihypertensive agents that have gained widespread use in clinical practice because of (1) antihypertensive efficacy similar to that of all agents classically employed to treat hypertension (i.e., calcium channel blockers [CGBs], beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, and diuretics), and (2) a placebo-like tolerability profile, which holds the promise of favorably impacting long-term compliance with antihypertensive treatment[1].

This placebo-like tolerability profile has been documented for all AIIRAs and should thus be regarded as a class-related feature[2]. Evidence has been produced, on the other hand, that compared with the first available AIIRA, losartan, subsequent agents of this class including candesartan, irbesartan, and telmisartan, may have greater blood pressure (BP) lowering ability, possibly because of differences in pharmacodynamic or pharmacokinetic properties[3].

Little information, however, is available on the comparative antihypertensive efficacy among the newer AIIRAs. The present study addressed this question by comparing two agents for which a greater angiotensin II antagonistic and BP-lowering effect has been demonstrated compared with losartan, irbesartan and valsartan[4]. Antihypertensive efficacy in the current analysis was assessed by BP measurements in the physician's office, at home, and by ambulatory monitoring to base results on multiple data collected in different environmental conditions.

METHODS AND SUBJECTS

Subjects were males and females aged between 18 and 75 years old with mild-to-moderate essential hypertension (defined as seated diastolic blood pressure [DBF] between 95 mmHg and 11OmmHg). Subjects were enrolled from 5 sites in Asser region (Appendix 1).

Study design:

This randomized, multicenter, double blind, parallel-group study compared the antihypertensive efficacy of irbesartan 150 mg with that of valsartan 80 mg, administered once daily for eight weeks. The primary objective was to compare the change from baseline in diastolic ABP at trough after eight weeks of treatment. Secondary objectives included comparing the changes from baseline in systolic ABP at trough; 24-h mean systolic and diastolic ABP; morning mean and evening mean systolic and

diastolic ABP; self-measured DBP and systolic blood pressure (SBP); and office-measured seated DBP and SBP and heart rate at trough. Another secondary objective was to determine the percentage of subjects whose office-measured BP at trough was normalized (DBP<90 mmHg) and who responded to therapy (i.e., whose office-measured DBP was normalized or changed from baseline ≥ 10 mmHg).

A medical history that included a complete physical examination and an electrocardiogram was obtained at screening. Brief physical examinations were performed at each visit, and a complete examination was performed again at study conclusion. Fasting blood samples were obtained for complete blood count and serum chemistries at screening and at study conclusion. All medications known to affect BP were prohibited. Subjects were withdrawn from participation in the study if, at any time, mean office BP measurements over a three-day period were SBP> 200 mmHg or DBP> 115 mmHg. Exclusion criteria included known or suspected secondary hypertension; office seated DBP> 110 mmHg or seated SBP> 200 mmHg; history of significant cardiac, hepatic, or renal disease; or uncontrolled diabetes, defined as fasting blood glucose > 180mg/dL (> IO mmol/L) or non-fasting blood glucose > 220mg/dL (> 11.2mmol/L), and clinically abnormal serum creatinine level, defined as ≥ 1.5mg/dL (≥132umoll/L).

After a three-weeks, single blind, placebo lead-in period, qualified subjects were randomized on a 1:1 ratio and entered eight weeks of double-blind treatment. At each study visit, subjects were monitored for adverse events. Subjects were instructed to arrive at the clinic in the morning, before taking their study medication.

Measurements and methods of analysis:

ABP measurements

24-hour ABE' readings were obtained with the same type of ABP monitor (model 90207; Spacelabs Medical, Redmond,) Washington, USA) for all subjects. The device was set to obtain readings every 15 minutes throughout a 24-h period. ABP readings were conducted at baseline and at Week8. During the 24 hour of ASP recording, measurements were obtained every three minutes, with the patients in controlled conditions at the clinic (seated, at rest, quiet, and not smoking).

Office BP and heart rate measurements

Seated office ABP and heart rate measurements were obtained at baseline and at Weeks 4 and 8 at trough. Subjects were instructed to arrive at the physician's office between 0700-l000 h, without having taken that day's study medication, eaten breakfast, smoked within two hours prior to the BP readings. All readings were taken 24 ± 3 hours following the last dose of study medication, in the dominant arm, and by the same observer. Blood pressure was measured with a standard, calibrated, mercury sphygmomanometer, following 10 minutes of rest in the seated position. Three consecutive BP measurements were obtained at least one minute apart and the values were averaged, after which heart rate was measured by pulse count

Home BP measurements

All subjects were trained to use a validated, calibrated, semi-automatic BP self-measurement device (Pressolink-T; Tam Telesante, Aix - en-Provence, France). The device includes an Omron HEM-705 BP monitoring device (Omron Healthcare, mc, Vernon Fulls, Illinois, USA), software for data collection, and hardware for data transmission. Self-measured BP was obtained at baseline and at Week 8. Blood pressure values were automatically recorded and stored by the BP self-measurement device. Subjects were instructed to take twice-daily (morning and evening) sequences of three BP readings over seven consecutive days for each of the two periods while seated. Three self-measurements were taken twice daily: in the morning on awakening (before breakfast and study drug intake) in a seated position, and in the evening at bedtime in a seated position

Summary statistics included mean, standard deviation, and mean plus standard deviation change from baseline for each treatment group. For the percentage of subjects who were normalized and who were responders, within-group 95% confidence intervals were calculated. The 95% confidence intervals and p values.

RESULTS

In this study, 375 subjects were randomized to receive either irbesartan 150 mg or valsartan 80 mg. Each group was balanced in demographic characteristics and baseline BP values (Table 1). The values for various BP changes induced by treatment are shown in Table 1. While both irbesartan and valsartan significantly reduced BP from baseline, in the 303 subjects included in the efficacy analysis for the study's primary objective, irbesartan produced a statistically greater reduction in mean diastolic ABP at trough (-6.73 mmHg vs. -4.84 mmHg, respectively; p - 0.035). Irbesartan also produced a statistically greater reduction in mean systolic ABP at trough (- 11.62 mmHg vs. -7.5 mmHg, respectively; $p < 0.01$). In addition, irbesartan caused a significantly greater reduction compared with valsartan in mean 24-h diastolic and systolic ABP ($p = 0.023$ and $p < 0.01$, respectively); mean daytime diastolic and systolic ABP ($p = 0.017$ and/) -0.02, respectively); and mean morning self-measured DBP and SBP ($p < 0.01$ for both).

There was no substantial difference between the two drugs for mean night-time ABP or for mean evening self-measured BP change from baseline. Hourly BP profile was lower with treatment than at baseline in both groups. During treatment, hourly BP values were usually lower in the irbesartan than in the valsartan group, the difference being more evident during the day than during the night (Table 1)

Consistent with other measures of BP-lowering efficacy, irbesartan, compared with valsartan,

produced significantly greater reductions in mean office-measured seated DBP and SBP at trough ($p < 0.01$ for both). Similar findings were obtained for mean office-measured standing BP

The percentage of subjects who were normalized was (52.5% and 38.2% for the irbesartan and valsartan groups, respectively. This difference was statistically significant in favor of the irbesartan group ($p = 0.004$). The percentage of responders was 63.9% and 44.3% for the irbesartan and valsartan groups, respectively, which was also statistically significant in favor of the irbesartan group ($p < 0.001$). There were no significant changes from baseline or between group differences in office trough seated or standing heart rate at Week 8.

Table 1: Baseline demographics and clinical characteristics

Characteristics	Valsartan 80 mg	Irbesartan 150 mg
n	180	170
Sex (male)	100	85
(Female)	80	85
Mean age (y)/(SD)	55.4 (9.9)	55.1 (9.7)
n	200	158
Mean weight (kg)/(SD)	81.8(14.5)	79.3 (12.4)
n	175	168
Trough 24th-hour ABP (SBP/DBP; mmHg)	150.0/95.7	148.3/94.2
[SD]	[9.9/15.0]	[9.2/14.3]
n	171	173
Mean ABP (SBP/DBP; mmHg)	143.8/89.1	142.2/88.2
[SD]	[12.0/8.3]	[12.7/8.3]
n	169	168
Seated office BP (SBP/DBP; mmHg)	158/100.8	159.3/100.7
[SD]	[14.1/4.6]	[13.6/4.2]
N	170	169
Self-measured morning BP (SBP/DBP; mmHg)	149.2/96.4	149.1/96.6
[SD]	[15.0/10.1]	[17.8/10.2]
n	159	147
Self-measured evening BP (SBP/DBP; mmHg)	149.8/95.2	148.8/94.3
[SD]	[14.6/10.2]	[17.1/9.8]
n	163	164
Seated office HR (bpm)	75.2	74.1
[SD]	[10.5]	[7.8]

ABP, ambulatory blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; HR, heart rate. Values are shown as mean ± standard deviation (SD). There were no statistically significant differences between groups at baseline.

DISCUSSION

In the present study, valsartan 80 mg and irbesartan 150 mg administered once daily over eight weeks significantly reduced BP in patients with mild-to-moderate hypertension. However, diastolic and systolic ABP at trough, 24 h average diastolic and systolic ABP, and daytime average diastolic and systolic ABP were all lowered to a significantly greater degree with irbesartan compared with valsartan. Office-measured systolic and diastolic BP and morning home self-measured BP were also lowered to a greater degree in patients taking irbesartan, as evidenced by greater rates of office BP normalization and response to treatment. It can be concluded that although both valsartan and irbesartan displayed antihypertensive efficacy, the duration and overall magnitude of the antihypertensive effect was greater for the latter agent than for the former.

The reductions in night-time and evening self-measured BP were not statistically different in the irbesartan and valsartan groups. This may be because the greater antihypertensive efficacy of one drug compared with another is not always consistent over 24 hours. However, the effect of the BP reduction was numerically greater in the irbesartan group compared with the valsartan group. It is possible that the lack of statistical significance was due to chance or to the fact that the smaller BP-lowering effect documented at night (because of the lower baseline BP value brought about by nocturnal hypotension) reduced the power necessary to give the smaller between-drug difference statistical support.

It is also important to note that 80 mg is the lowest available dose of valsartan (typical available doses of valsartan are 80mg, 160mg, and 320mg), while with irbesartan 150mg is a median dose in this agent's dose spectrum (irbesartan is available in 75 mg, 150 mg, and 300 mg doses). Although valsartan 80 mg and irbesartan 150 mg may be the most commonly prescribed doses in clinical practice, they may not be pharmacodynamically equivalent.

Several other points deserve to be discussed. First, irbesartan demonstrated a greater antihypertensive effect than valsartan in the morning period, when the incidence of cardiac and cerebrovascular events are at their zenith[5] due to the arousal-related rise in BP, heart rate, and platelet aggregation and the concomitant reduction in fibrinolytic activity. Second, ambulatory BP measurements are frequently used in combination with office-measured BP readings to evaluate the efficacy of antihypertensive therapy[6]. Compared with office measurements, ABP measurements offer

a greater level of prognostic information[7] and greater reproducibility[8] without the confounding effect of the variable BP increases associated with BP measurements performed by a doctor[9] or a nurse[10]. In contrast, self-measured BP readings are employed less frequently in antihypertensive drug studies, despite the evidence that they also have a good reproducibility[11].

In the present study, self-measured BP readings yielded similar results to those obtained with ABP monitoring, suggesting a potential role for this approach in antihypertensive drug studies.

Finally, our study does not provide information on the reasons why the antihypertensive effect of irbesartan was greater than that of valsartan. However, the difference in efficacy could be explained by inter-agent differences with respect to bio-availability, half-life, and completeness and duration of angiotensin II blockade reported in comparative pharmacodynamic and pharmacokinetic studies. This study also does not answer the question of whether these differences in antihypertensive efficacy are maintained with different doses of the two drugs. It provides further evidence, however, that within the AHRA drug class, BP-lowering efficacy between agents may not be invariably homogeneous.

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Appendix 1. Study sites, Asser central hospital, Abha general hospital, Abha private hospital, Alahly khamis meshat hospital and Saudi German hospital, Abha

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دراسة رقابية و مقارنة وفاعلية خافضات ارتفاع ضغط الدم للمضادات مستقبلات أنجوتنسن من النوع II الأريزارتان و الفالزرتان

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تم حديثا تطوير مجموعة مضادات مستقبلات الإنجوتيسين المضادة لإرتفاع ضغط الدم و التى لاقت إستخداماً واسعاً فى التطبيقات السريرية .

وكان أول هذه المجموعة لوزارتان ثم تلى ذلك الكاوززرتان إريبزارتان و تلجيزارتان ذات قدره عالية لتخفيض الضغط حيث أن هناك نقص فى معلومات للمقارنة بين هذه المجموعة وهذه الدراسة تجيب عن ذلك السؤال بمقارنة إربيزارتان وفالزرتان وتم إستخدام معدل إنخفاض ضغط الدم مقياس ضغط الدم فى مكتب الطبيب و فى المنزل و فى الطوارئ فى أجواء مختلفة المرض كانو رجال و إناث فى عمر ١٨- ٧٥ يعانون من إرتفاع ضغط الدم الأولى فى الحالة البسيطة والمتوسطة والمتعارف عليها الضغط الإنبساطى فى حالة جلوس بين ٩٥- ١١٥ ملم زئبق و تم تسجيلهم من خمس مستشفيات فى محافظة عسير هذه الدراسة العشوائية ثم مقارنة فاعلية إيزارتان ١٥٠ ملجم مع فالزرتان ٨٠ مجم تم تعاطيهما مرة واحدة لمدة ٨ أسابيع و كان الهدف الأول مقارنة الطوارئ بعد مرور ٨ أسابيع من العلاج دون أخذ الدواء فى ذلك اليوم و الهدف الثانى مقارنة التغير فى الضغط الإنقباضى عن القراءة الأولية فى الطوارئ دون إعطاء الدواء اليومى متوسط قراءة الضغط الإنبساطى والإنقباضى فى الطوارئ خلال ٢٤ ساعة متوسط القرأة الصباحية و المسائية للضغط الإنبساطى والإنقباضى فى الطوارئ متوسط القياس الشخص للضغط الإنبساطى و الإنقباضى و كذلك متوسط القياسات الإنبساطية والإنقباضية وسرعة ضربات القلب فى العيادة.

الهدف الآخر تعيين نسبة المئوية للأشخاص الذى عاد الضغط الإنبساطى إلى أقل من ٩٠ ملم زئبق أو أقل من قيمة ١٠ أكثر ملم زئبق عن القيمة الأولية بينما نجد أن إريبزارتان وفالزرتان إنخفاض ضغط الدم كان واضحا عن القراءة الأولى فى ٣٠٣ مريض كان قدرة الإريزارتان فى تخفيض الضغط الإنبساطى عن الفالزرتان إحصائيا كبير دون أخذ الدواء بعد الأسبوع الثانية (٦،٧٣ ملم زئبق بالمقارنة ٤،٨٤ ملم زئبق) على التوالى .

أما الإنقباض فكان (- ١١،٦٢ ملم زئبق) بالمقارنة (- ٧،٥ ملم زئبق ($p < ٠،٠١$) و كان كذلك متوسط القياس لمدة ٢٤ ساعة فى الطوارئ($p = ٠،٢٣$) ، ($p< ٠،٠١$) على التوالى و كذلك المقارنة من العقارين فى المتوسط قرأة قياس الضغط مساءا الإنبساطى و الإنقباضى ($p = ٠،٠١٧$ و $p=٠،٠٢$)على التوالى و كذلك بالنسبة لمتوسط القراءات الصباحية و الشخصية كان الإنبساطى و الإنقباضى ($p < ٠،٠١$) لكليهما