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Effectiveness and safety of eprosartan on pulse pressure for the treatment of hypertensive patients

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SUMMARY

A multicentre, prospective, non-comparative open-label study was conducted to assess the effect of eprosartan, 600 mg/day, on pulse pressure (PP) in patients with hypertension (stage I or II, Joint National Committee, sixth report) treated in the primary care setting, as well as safety and compliance. The duration of treatment was 16 weeks. Eprosartan decreased PP (−13 mmHg), systolic blood pressure (SBP) (−26 mmHg), diastolic blood pressure (DBP) (−13 mmHg) and mean arterial pressure (MAP) (−17.4 mmHg) significantly ($p < 0.0001$). The PP/MAP ratio changed significantly from 62 to 59%, so that the reduction of PP was 3% higher than the overall decrease in MAP. Twenty adverse events, mostly gastrointestinal complaints, were recorded in 12 patients (1.9%). Compliance with treatment at the end of the study was 94%. Eprosartan was a well-tolerated and an effective drug in reducing PP, SBP and DBP below the recommended levels in patients with mild-to-moderate essential hypertension, allowing a high therapeutic compliance.

Keywords: Hypertension; pulse pressure; eprosartan

INTRODUCTION

One of the problems that is becoming more frequent in clinical practice is the increase in pulse pressure (PP) when the difference between diastolic blood pressure (DBP) and systolic blood pressure (SBP) increases, despite a rise in the absolute values of both parameters. Isolated systolic hypertension is a particular case of this phenomenon that occurs when DBP levels remain within normal limits and there is only an increase in SBP. The prevalence of isolated systolic hypertension is growing in association with ageing of the population, being a highly prevalent condition in subjects older than 70 years of age. Although the natural history of hypertensive disease over the lifespan seems to be the most important contributing factor, the prevalence of isolated systolic hypertension increases in the presence of other risk factors, particularly diabetes mellitus (1–4).

Currently, there is increasing evidence that even small elevations of SBP are associated with a proportional increase in the cardiovascular risk. In fact, SBP is better predictor of cardiovascular disease than DBP (5–8). In addition, patients are at the highest risk for cardiovascular morbidity and mortality when the difference between DBP and SBP is maximal, i.e. when the PP reaches the highest increase. Therefore, there is a need for effective antihypertensives on reduction of the difference between both components of blood pressure.

On the other hand, the response of SBP to antihypertensive therapy is lower than that obtained on the other component of blood pressure (9). Eprosartan is a novel orally active A-II receptor blocker that is highly selective for the type 1 (AT_1) receptor that is able to elicit a higher reduction of SBP than other antihypertensive drugs (10,11). A postmarketing drug-surveillance study was conducted in Spain to determine the effectiveness and safety of eprosartan 600 mg once daily in patients with hypertension. The goal of the present study was to examine the effect of this medication on the pulsatile component (PP) of blood pressure.

PATIENTS AND METHODS

This was a multicentre, prospective, observational, non-comparative, open-label trial that was designed to assess the effectiveness and safety of a single daily oral dose of eprosartan 600 mg given over a period of 16 weeks. The study was conducted in Spain in the outpatient setting. Because of the design of the study, calculation of the sample size was not applicable. Between April 2002 and August 2003, a representative sample of hypertensive patients were consecutively recruited by 140 family physicians, six patients each.

Male and female patients aged ≥18 years with treated or untreated essential hypertension, stages I or II according to classification criteria of the sixth report of the Joint National

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Committee (8), defined as SBP in the range of 140–179 mmHg and/or DBP 90–109 mmHg, were eligible. Inclusion criteria included the following: evidence of hypertension on three separate blood pressure measurements; poorly controlled hypertension with previous antihypertensive drugs, or need to add eprosartan to the current medication to lower blood pressure, or need to switch to eprosartan due to adverse events related to the antihypertensive drug; and no history of acute cerebrovascular accident, acute myocardial infarction or any other severe cardiovascular complication within 6 months. The following exclusion criteria were applied: SBP $\geq$180 mmHg or DBP $\geq$110 mmHg, known hypersensitivity or history of severe adverse effects to angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists, serum creatinine concentration $>$2 mg/dl and presence of any contraindication for prescribing eprosartan as stated in the technical form of the product. Pregnant women, nursing mothers or women of childbearing potential not using adequate methods of contraception were also excluded.

Readings of SBP and DBP were taken with a semiautomatic, printer-equipped, digital sphygmomanometer (OMRON 705CP) with the patient seated in a chair with back supported after 5 min of quit rest. A visit blood pressure was the average of two separate measurements taken by the examining physician (a third measurement was obtained when there was a difference of 5 mmHg between the two readings). Printed blood pressure readings were attached to the care report forms.

Adequate control of blood pressure was defined as SBP $\leq$140 mmHg and/or DBP $\leq$90 mmHg and the percentage of patients with a reduction $\geq$10 mmHg of SBP and/or DBP. PP was calculated as the difference between SBP and DBP, and mean arterial pressure (MAP) as the DBP + 1/3(PP). The PP/MAP ratio was also calculated.

Patients were assessed at baseline and at 4, 8, 12 and 16 weeks after commencement of treatment with eprosartan. At each visit, blood pressure and pulse rate were measured, treatment compliance was checked and the incidence and intensity of adverse events were recorded. During the clinic visits, study therapy could be uptitrated by adding a second antihypertensive drug if blood pressure was still not controlled. Antihypertensive drugs with direct action on the rennin–angiotensin system were not allowed. All adverse events were designated by the investigator as either drug related or not drug related. At the end of the study, effectiveness and safety of treatment with eprosartan was assessed by the patients and the investigators as 'poor', 'regular', 'good' and 'very good'. A flow chart of the study is shown in Table 1.

The primary endpoints were the following: changes of PP after 16 weeks of antihypertensive treatment with eprosartan, decrease of SBP and DBP (mmHg) at the end of treatment and percentage of patients with adequate control of blood pressure. Secondary endpoints included the incidence of volunteered elicited adverse events, percentage and causes of withdrawal of antihypertensive medication and percentage of patients compliant with the study medication (between 80 and 110% of daily intakes).

Statistical Analysis

Statistical analyses were performed for the full analysis set population or intention-to-treat (patients who had eprosartan prescribed at the baseline visit and had at least a post-treatment value for the endpoint of PP) and the safety data set population (patients included in the study who had received at least one dose of eprosartan).

Quantitative variables are expressed as mean and standard deviation (SD). The Student's *t*-test for paired and unpaired data was used to assess treatment effects on continuous variables. Categorical variables were analysed with the χ^2 test. The analysis of covariance (ANCOVA) was used to assess the effect of eprosartan in a prespecified subset of the study population divided according to age dichotomised at 65 years. Statistical significance was set at $p < 0.05$. The Statistical

Table 1 Flow chart of the study

Trial periods	*Visit 1 (baseline)*	*Visit 2*	*Visit 3*	*Visit 4*
Day	0	28 (±7)	56 (±7)	112 (±7)
Inclusion/exclusion criteria	×			
Medical history	×			
Physical examination	×			
Systolic blood pressure (SBP)	×	×	×	×
Diastolic blood pressure (DBP)	×	×	×	×
Pulse pressure (SBP − DBP)	×	×	×	×
Heart rate	×	×	×	×
Dispense study medication	×			
Check compliance		×	×	×
Adverse events		×	×	×
Assessment of effectiveness and safety of treatment by the patient				×
Assessment of effectiveness and safety of treatment by the investigator				×

Analysis Systems (SAS Institute, Cary, NC, USA) statistical software package for Windows was used to analyse the data.

RESULTS

The study population consisted of 648 patients (safety data set population), 556 (85.8%) of which were evaluable at the end of the study period for the effectiveness of antihypertensive treatment. Of these, 46.7% were men and 53.3% women, with a mean (SD) age of 63 (11.6) years. A total of 246 patients were older than 65 years. Treatment with eprosartan was indicated because of poorly controlled hypertension with previous antihypertensive agents in 59.6% of patients, *de novo* diagnosis of essential hypertension in 30.3%, adverse effects related to previous antihypertensive medication in 9.6% and other reasons in 6.1%. Table 2 shows cardiovascular risk factors and baseline values of SBP, DBP, MAP and PP.

Table 3 shows changes in blood pressure and heart rate during the study period. SBP decreased from a mean (SD) level of 163.2 mmHg (15.3) at baseline to 137.3 mmHg (14.4) at the end of the study, DBP from 92.2 mmHg (10.0) to 79.3 mmHg (7.9), MAP from 115.8 mmHg (9.4) to 98.6 mmHg (8.8) as shown in Figure 1 and PP from 71.0 mmHg (15.9) to 58.0 mmHg (12.2). All these differences were statistically significant ($p < 0.0001$). As shown in Figure 2, final reduction of blood pressure was −26 mmHg for SBP (15.3% of the initial value), −13 mmHg for DBP (13.9% of the initial value) −17.4 mmHg for MAP (14.6% of the initial value) and −13 mmHg for PP (15.0% of the initial value).

The overall percentage of patients with adequate control of blood pressure was 91.6% for DBP (≤90 mmHg), 60.2% for SBP (≤140 mmHg) and 58.4% for both (Figure 3). In 26% of patients, a second antihypertensive drug was added during the course of the study. The proportion of patients with adequate control of blood pressure at 4, 8 and 16 weeks was 36.3, 54.5 and 61.3% in the eprosartan monotherapy group compared with 12.2, 17.2 and 25.9%, respectively, in those initially treated with eprosartan to which a second antihypertensive was added. These differences at all study visits were statistically significant in favour of the monotherapy group ($p < 0.001$). However, when the groups of eprosartan monotherapy and combined therapy (eprosartan initially administered to the current medication to lower blood pressure) were compared, significant differences in the percentage of patients in whom blood pressure was adequately controlled at the end of the study were not found, although the proportion was slightly higher in those given combined therapy (66 vs. 61%).

In the assessment of the results of treatment with eprosartan, 82% of investigators and 88% of patients rated the efficacy of the antihypertensive medication as 'good' or 'very good'.

Compliance with treatment at the end of the study was 94%.

Table 2 Baseline data in the 566 patients included in the efficacy analysis (blood pressure measurements before treatment with eprosartan 600 mg once daily for 16 weeks)

Characteristics	*Percentage of patients*	*Means (SD)*
Age (years)		63 (11)
Patients older than 65 years	43.5	
Body mass index (kg/m^2)		28.50 (3.91)
Previously untreated	40.7	
Previously treated	59.4	
Cardiovascular risk factors		
Current cigarrete smoking	13.5	
Alcohol use (>80 g/day)	26.1	
Hyperlipidaemia	41.9	
Diabetes mellitus	20.8	
Left ventricular hypertrophy	14.3	
Family history of cardiovascular disease	20.3	
Ischaemic heart disease	6.8	
Heart failure	4.2	
Transient ischaemic attack	4.3	
Peripheral artery disease	10.7	
Systolic blood pressure (mmHg)		163.1 (15.4)
Diastolic blood pressure (mmHg)		92.4 (9.6)
Mean arterial pressure		115.9 (9.2)
Pulse pressure (mmHg)		71.0 (15.8)
Heart rate (beats/min)		75.5 (11.6)

Efficacy in Elderly Patients

As shown in Table 4, when patients were divided into two groups according to age, treatment with eprosartan was associated with a statistically significant reductions of SBP, DBP, MAP and PP ($p < 0.0001$), both in the subset of patients aged 65 years or older and in the younger group. However, differences between these subsets of patients in all blood pressure components throughout the study period were not observed. PP showed a final decrease of −15.5 mmHg (18.4) in older patients compared with −11.0 mmHg (14.9) in patients under 65 years (Figure 4). On the other hand, there were no statistically significant differences in the PP/MAP ratio according to age (Figure 5).

Adverse Events

Twelve patients presented at least one adverse event (1.8%), with a total of 20 adverse events. The most common complaints were vomiting, diarrhoea, epigastric pain, dizziness and headache. Adverse events were of mild intensity, but seven patients (1.1%) discontinued the study for this reason. One patient treated with eprosartan and doxazosin presented a severe adverse event (0.1%) possibly related to the study

Table 3 Changes in blood pressure and heart rate during the study period

				Difference compared with baseline		
Data	*n*	*Mean*	*SD*	*Mean*	*SD*	*p-value*
Systolic blood pressure						
Baseline	566	163.17	15.28	0.00		
Week 4	546	145.99	15.46	−17.15	16.80	< 0.0001
Week 8	537	141.21	15.84	−21.95	17.41	< 0.0001
Week 16	525	137.29	14.37	−26.04	16.93	< 0.0001
Diastolic blood pressure						
Baseline	566	92.18	9.99	0.00		
Week 4	546	83.39	9.46	−8.86	10.26	< 0.0001
Week 8	537	80.92	8.07	−11.42	10.61	< 0.0001
Week 16	525	79.26	7.89	−13.05	10.89	< 0.0001
Pulse pressure (PP)						
Baseline	566	70.99	15.88	0.00		
Week 4	546	62.60	13.92	−8.29	16.09	< 0.0001
Week 8	537	60.29	13.77	−10.53	16.26	< 0.0001
Week 16	525	58.03	12.22	−12.99	16.58	< 0.0001
Mean arterial pressure (MAP)						
Baseline	566	115.84	9.40	0.00		
Week 4	546	104.26	9.81	−11.62	10.34	< 0.0001
Week 8	537	101.02	9.22	−14.93	10.83	< 0.0001
Week 16	525	98.60	8.78	−17.38	10.66	< 0.0001
PP/MAP ratio						
Baseline	566	0.62	0.14	0.00	0.00	
Week 4	546	0.60	0.13	−0.01	0.14	0.0553
Week 8	537	0.60	0.12	−0.02	0.14	0.0045
Week 16	525	0.59	0.11	−0.03	0.15	< 0.0001
Heart rate (beats/min)						
Baseline	548	75.46	11.62	0.00		
Week 4	528	74.66	10.42	−0.76	11.90	0.1427
Week 8	510	73.70	10.02	−1.82	11.53	0.0004
Week 16	491	74.17	10.19	−1.38	12.35	0.0136

drug, with asthenia, vomiting with probable haematic content, diarrhoea and low haematocrit value that required blood transfusion. Antihypertensive medication was not withdrawn, and recovery of the patient was uneventful.

Ninety-three per cent of physicians and 92% of patients considered that safety of antihypertensive therapy was 'good' or 'very good'.

DISCUSSION

Hypertension remains one of the most common medical conditions, predisposing patients to cardiovascular morbidity and mortality. Despite extensive clinical evidence of the benefit of optimal blood pressure control in patients with

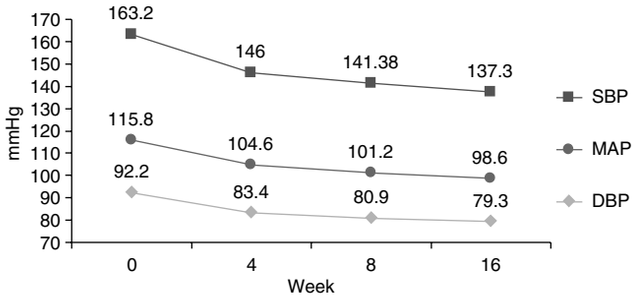

Figure 1 Time course of blood pressure levels during treatment with eprosartan (SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure)

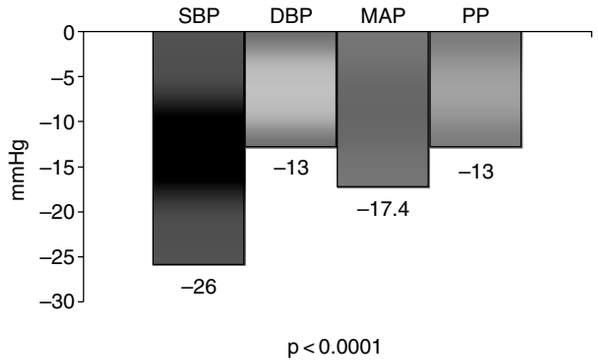

Figure 2 Decrease in blood pressure with eprosartan (SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure)

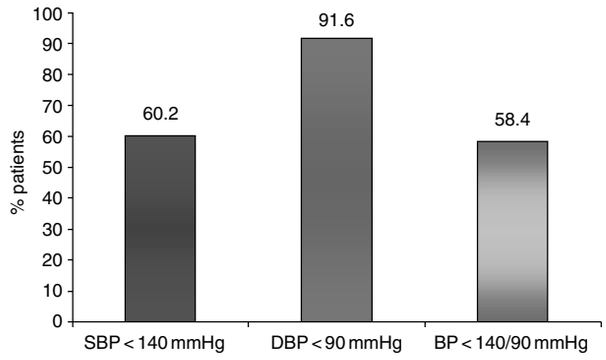

Figure 3 Percentage of patients with adequate control of blood pressure (BP) at the end of the study (SBP, systolic blood pressure; DBP, diastolic blood pressure)

hypertension, recommended target blood pressures are rarely achieved. Blood pressure is inadequately controlled in a large percentage of patients, but it is particularly unsatisfactory in the elderly and in patients with high cardiovascular risk (9). Angiotensin receptor antagonists are a relatively new class of antihypertensive agents and have the therapeutic advantage of efficacy, excellent tolerability and a good record of compliance (10). The renin–angiotensin–aldosterone system can also be inhibited by angiotensin II (A-II) receptor blockers, and this approach may avoid some of the side effects, which may occur with ACE inhibitors (11). On the other hand, it has been shown that angiotensin receptor antagonists might have superior efficacy to that of other agents in certain populations, such as patients with chronic heart failure (12), left ventricular hypertrophy (13), nephropathy due to type 2 diabetes (14), cerebral vascular disease (15) and at risk of cardiovascular events after myocardial infarction (16).

Within the class of A-II blockers, eprosartan differs from other currently available agents in terms of chemical structure, as it is a non-biphenyl, non-tetrazole, non-peptide antagonist with a dual pharmacological mode of action. Eprosartan acts at vascular AT_1 receptors (postsynaptically) and at presynaptic AT_1 receptors, where it inhibits sympathetically stimulated

Table 4 Changes in blood pressure and heart rate in patients aged 65 years or older and younger than 65 years

	< 65 years			*≥65 years*			
Data	*Mean*	*SD*	*p-value**	*Mean*	*SD*	*p-value**	*p-value†*
Systolic blood pressure							
Baseline	161.84	13.89		164.75	16.80		
Week 4	145.18	15.37	< 0.0001	146.59	15.41	< 0.0001	0.8698
Week 8	139.82	15.23	< 0.0001	142.43	16.36	< 0.0001	0.2226
Week 16	136.65	13.94	< 0.0001	137.88	15.01	< 0.0001	0.7136
Diastolic blood pressure							
Baseline	94.02	9.35		89.96	10.44		
Week 4	84.41	9.22	< 0.0001	81.98	9.59	< 0.0001	0.4314
Week 8	81.38	7.75	< 0.0001	80.11	8.30	< 0.0001	0.8946
Week 16	79.64	7.66	< 0.0001	78.66	8.12	< 0.0001	0.9349
Pulse pressure (PP)							
Baseline	67.82	14.77		74.79	16.49		
Week 4	60.77	13.80	< 0.0001	64.61	13.91	< 0.0001	0.3021
Week 8	58.43	13.28	< 0.0001	62.31	14.10	< 0.0001	0.2058
Week 16	57.01	11.84	< 0.0001	59.22	12.84	< 0.0001	0.5907
Mean arterial pressure (MAP)							
Baseline	116.63	8.61		114.89	10.31		
Week 4	104.67	9.65	< 0.0001	103.52	9.87	< 0.0001	0.6967
Week 8	100.86	8.84	< 0.0001	100.88	9.54	< 0.0001	0.3801
Week 16	98.64	8.53	< 0.0001	98.40	9.08	< 0.0001	0.6189
PP/MAP ratio							
Baseline	0.58	0.13		0.65	0.14		
Week 4	0.58	0.13	0.8975	0.63	0.14	0.0086	0.1447
Week 8	0.58	0.12	0.7935	0.62	0.12	0.0004	0.1615
Week 16	0.58	0.11	0.4783	0.60	0.12	< 0.0001	0.3832
Heart rate (beats/min)							
Baseline	75.84	11.94		75.06	11.31		
Week 4	75.25	10.28	0.4191	74.09	10.54	0.2834	0.3206
Week 8	73.70	10.28	0.0080	73.74	9.82	0.0305	0.8526
Week 16	73.66	9.59	0.0082	74.84	10.92	0.5801	0.1391

*Intragroup Student's *t*-test;
†Analysis of covariance (ANCOVA).

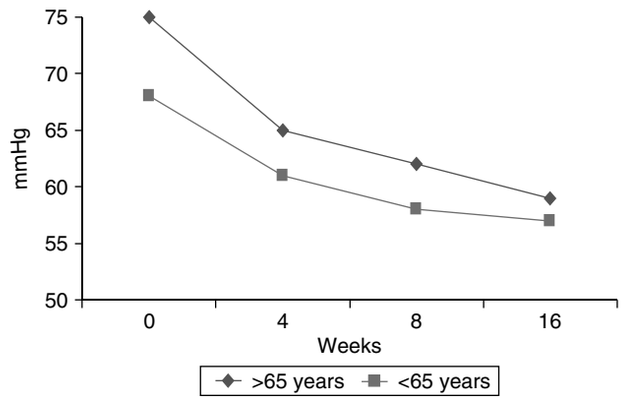

Figure 4 Time course of pulse pressure in patients treated with eprosartan divided according to age. Differences were not statistically significant

noradrenaline release. This dual pharmacological mode of action observed on post- and presynaptic AT_1 receptors, not seen to such an extent with other A-II blockers, would be of special interest when lowering SBP (and PP) in patients with systolic forms of hypertension. Eprosartan significantly reduces SBP and to a greater extent than the ACE inhibitor enalapril (6). Moreover, eprosartan appears to be a safe and well-tolerated drug, without significant drug interactions, which is important due to the likelihood of patients taking concomitant medication, and with a very low incidence of side-effects (17–19). In the present study, the incidence of adverse events related to the study medication was also very low. The excellent safety profile of eprosartan contributes, in turn, to the high rate of compliance with treatment observed during the follow-up of patients.

With regard to changes of PP and SBP after 16 weeks of antihypertensive treatment with eprosartan, two primary endpoints of the study, there was a statistically significant reduction of both parameters as compared with baseline. This effect observed in the overall study population was also found in the subset of patients aged 65 years and older. In older patients, PP is an indicator of large-artery stiffness and becomes a dominant factor predicting cardiovascular risk (3). PP may be the most reliable blood pressure indicator when systolic hypertension is accompanied by normal or low DBP. This may have important implications because isolated systolic hypertension is the most common type of hypertension among untreated adults >50 years old (2). In spite of higher PP, the response of aged patients to eprosartan was not impaired by this basal status. The proportion of patients with adequate control of blood pressure increased significantly during the course of the study, with 61.3% at the last assessment. There were no significant differences in the percentage of patients with controlled blood pressure at the end of the study regarding the use of eprosartan monotherapy or combined therapy, although the percentage was slightly higher in the combined therapy group (66 vs. 61%). This finding is consistent with results of other studies in which additional pressure control was achieved when eprosartan was given in combination with hydrochlorothiazide (20–22).

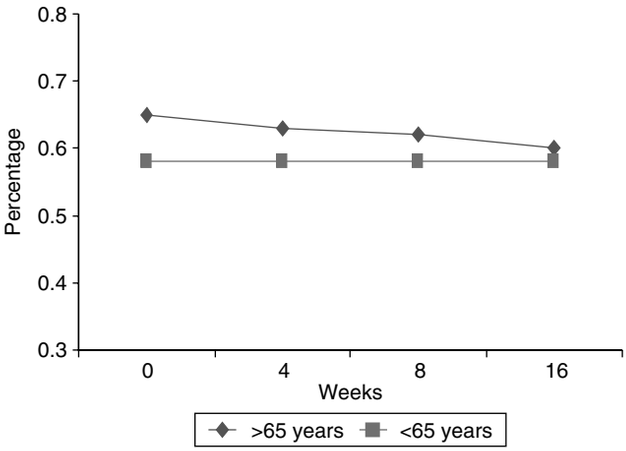

Figure 5 Time course of pulse pressure/mean arterial pressure (PP/MAP) ratio in patients treated with eprosartan divided according to age. Differences were not statistically significant

This study confirms the effectiveness and safety of eprosartan 600 mg once daily in patients with mild-to-moderate hypertension. Although controlled clinical trials provide essential information about the efficacy and safety of a drug, the experimental conditions of such trials do not mimic everyday clinical practice. Therefore, once efficacy and safety have been established in controlled trials, it is both useful and informative for clinicians to subject the drug to a trial that more closely reflects actual conditions of use in a large patient population. This was the objective of the present open-label surveillance study.

In summary, in poorly controlled patients with mild-to-moderate hypertension and in patients with newly diagnosed high blood pressure, eprosartan was an effective agent for lowering SBP and DBP. In comparison with reduction of MAP, eprosartan may achieve a greater effect on PP. Eprosartan had a beneficial systolic effect in elderly patients. The drug showed a good safety profile and a few number of adverse events. Severity of the increase in PP associated with age does not seem to modify the effect of the drug in reducing elevated blood pressure.

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REFERENCES

1 Van Bortel LM, Struijker-Boudier HA, Safar ME. Pulse pressure, arterial stiffness, and drug treatment of hypertension. *Hypertension* 2001; **38**: 914–21.
2 Sagie A, Larson MG, Levy D. The natural history of borderline isolated systolic hypertension. *N Engl J Med* 1993; **329**: 1912–7.
3 Franklin SS, Khan SA, Wong ND et al. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. *Circulation* 1999; **100**: 354–60.
4 Benetos A, Zureik M, Morcet J et al. A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is associated with a higher cardiovascular mortality in men. *J Am Coll Cardiol* 2000; **35**: 673–80.
5 Macia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. *J Hypertens* 2002; **20**: 1461–4.
6 Sega R. Efficacy and safety of eprosartan in severe hypertension. Eprosartan Multinational Study Group. *Blood Press* 1999; **8**: 114–21.
7 De la Sierra A, Muñoz A, Arcos E et al. Efecto del tratamiento con eprosartan sobre la presión de pulso. Factores predictores de respuesta [Artice Spanish]. *Hipertensión* 2003; **20**: 56–62.
8 The sixth report of the Joint National Committee on prevention, detection evaluation and treatment of high blood pressure. *Arch Intern Med* 1997; **157**: 2413–46.
9 Cocchi R, Degli Esposti E, Ruffo P et al. Cardiovascular risk in hypertensive patients: results of the Pandora project. *J Nephrol* 2002; **15**: 29–35.
10 McInnes GT. Angiotensin II antagonists in systolic blood pressure control. *Hosp Med* 2001; **62**: 773–7.
11 Riulope L, Jäger B. Eprosartan for the treatment of hypertension. *Expert Opin Pharmacother* 2003; **4**: 107–14.
12 Pfeffer MA, Swedberg K, Granger CB et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003; **362**: 759–66.
13 Okin PM, Devereux RB, Jern S et al. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study. *Circulation* 2003; **108**: 684–90.
14 Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851–60.
15 Kjeldsen SE, Dahlof B, Devereux RB et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. *JAMA* 2002; **288**: 1491–8.
16 Pfeffer MA, McMurray JJ, Velazquez EJ et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349**: 1893–906.
17 Gradman AH, Gray J, Maggiacomo F et al. Assessment of once-daily eprosartan, an angiotensin II antagonist, in patients with systemic hypertension. Eprosartan Study Group. *Clin Ther* 1999; **17**: 129–36.
18 Gavras I, Gavras H. Effects of eprosartan versus enalapril in hypertensive patients on the renin-angiotensin-aldosterone system and safety parameters: results from a 26-week, double-blind, multicentre study. Eprosartan Multinational Study Group. *Curr Med Res Opin* 1999; **15**: 15–24.
19 Hedner T, Himmelmann A. The efficacy and tolerance of one or two daily doses of eprosartan in essential hypertension. The Eprosartan Multinational Study Group. *J Hypertens* 1999; **17**: 129–36.
20 Sachse A, Verboom CN, Jager B. Efficacy of eprosartan in combination with HCTZ in patients with essential hypertension. *J Hum Hypertens* 2002; **16**: 169–76.
21 Punzi HA, Punzi CF. Once-daily eprosartan mesylate in the treatment of elderly patients with isolated systolic hypertension: data from a 13-week double-blind, placebo-controlled, parallel, multicenter study. *J Hum Hypertens* 2004; **18**: 655–61.
22 Puig JG, Lopez MA, Bueso TS et al. Clinical profile of eprosartan. *Cardiovasc Drug Ther* 2002; **16**: 543–9.

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