Effects of eprosartan on target organ protection

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Abstract: Hypertension is the most important cardiovascular risk factor for stroke. Blood pressure reduction by antihypertensive treatment is clearly efficacious in the prevention of stroke (both primary and secondary), although no clear differences have yet been observed between antihypertensive drug classes. However, a recent study reported the clear superiority of the angiotensin-receptor blocker eprosartan over the calcium channel blocker nitrendipine in cardiovascular protection of hypertensive patients with a previous stroke. Comparative studies using angiotensin-receptor blockers have also suggested the superiority of this class of drugs on primary stroke prevention. This effect may be linked to their beneficial actions on left ventricular hypertrophy, atrial enlargement, and supraventricular arrhythmias, endothelial dysfunction, inflammation, and remodelling, as well as a direct neuroprotective effect mediated through the stimulation of the angiotensin II type-2 receptor. In addition, a sympathoinhibition observed with the renin–angiotensin system blockers and particularly demonstrated with eprosartan, may help to explain the better cardiovascular and cerebrovascular protection in comparison with the calcium antagonist nitrendipine.

Keywords: eprosartan, angiotensin-receptor blockers, hypertension, stroke, organ protection

Introduction

Cardiovascular disease is the leading cause of death and disability in developed countries and arterial hypertension is one of the most powerful risk factors for developing such cardiovascular complications (Lewington 2002). The prevalence of hypertension is increasing and reaches more than 50% in people aged over 60 (Wolf-Maier et al 2003). The residual life-time risk for developing hypertension is higher than 90% (Vasan et al 2002).

The pathogenesis and pathophysiology of essential hypertension is complex and involves both genetic and environmental aspects. However, it has become clear that both the renin–angiotensin system (RAS) and the sympathetic nervous system (SNS) play important roles in the development and maintenance of elevated blood pressure (BP) values and in the pathogenesis of target organ damage. Bearing this pathogenetic complexity in mind, therapeutic approaches for hypertension and cardiovascular diseases include the use of various, very different drug classes, including diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blockers (ARB) (Chobanian et al 2003; GC 2003).

Angiotensin-receptor blockers selectively antagonize the angiotensin II type 1 (AT_1) receptor and counteract most of the deleterious actions of angiotensin II. Eprosartan is an ARB with a special chemical structure that may be relevant to its mechanism of action. The pharmacological properties and clinical efficacy and safety of eprosartan have been previously reviewed (Plosker and Foster 2000; Robins and Scott 2005).

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In June 2005, an important study reported the superiority of eprosartan over the calcium channel blocker nitrendipine in cardiovascular protection of hypertensive patients with a previous stroke (Schrader et al 2005). The present paper reviews the main findings of this trial and tries to answer some questions posed after its publication. The importance of stroke prevention by ARB in general and eprosartan in particular are also discussed.

The importance of stroke and the MOSES study

Stroke is the most frequent cardiovascular complication in hypertensive patients older than 60. A retrospective analysis of clinical trials in hypertensive patients published from 1991 to 2000 that included 59 550 randomized patients revealed that the total number of strokes (2533 events; 4.25%) clearly exceeded coronary events (1927 events; 3.24%) (Kjeldsen et al 2001). Blood pressure reduction and control is extremely important to prevent both stroke appearance (Collins et al 1990; Staessen et al 2000) and recurrence (PROGRESS 2000). Comparative trials and meta-analyses suggest that among different antihypertensive treatments, calcium channel blockers seem to represent the most powerful option for stroke prevention (Turnbull 2003; Angeli et al 2004).

No comparative trials between different antihypertensive drug classes were reported before the Morbidity and Mortality after Stroke, Eprosartan compared with Nitrendipine for Secondary Prevention (MOSES) study. The MOSES investigators hypothesized that for the same BP reduction, the ARB eprosartan would be superior to the calcium channel blocker nitrendipine in the cardiovascular protection of hypertensive patients with a previous stroke. Nitrendipine was chosen as a comparative drug on the basis of the cardiovascular and cerebrovascular protection observed in two trials of patients with isolated systolic hypertension (Staessen et al 1997; Wang et al 2000) and, as mentioned above, due to the fact that calcium channel blockers seem to be more protective against stroke than other antihypertensive drug classes.

A total of 1405 patients with a previous cerebrovascular event (ischemic stroke, transitory ischemic attack, or cerebral hemorrhage) who were hypertensive (by both clinical measurements and ambulatory BP monitoring) were randomized to receive eprosartan 600 mg once daily or nitrendipine 10 mg once daily. Higher doses or combination therapy (excluding ARB and calcium channel blockers) were used in order to achieve a target BP lower than 140/90 mmHg.

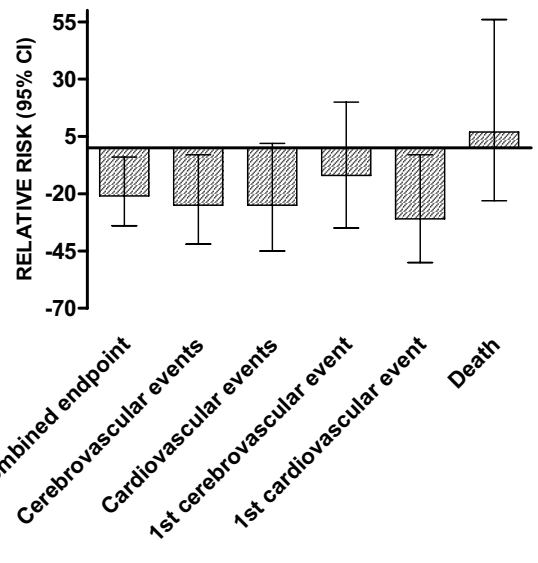

Figure 1 Effect of eprosartan compared with nitrendipine in various endpoints in the MOSES study.
Abbreviations: CI, confidence interval; MOSES, Morbidity and Mortality after Stroke, Eprosartan compared with Nitrendipine for Secondary Prevention study.

The primary endpoint was the composite of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events.

The principal results of the MOSES trial revealed the superiority of eprosartan over nitrendipine in the primary endpoint (Figure 1). There were 206 primary endpoints in the eprosartan group (incidence density per 100 person-years [ID] of 13.25) and 255 primary endpoints in the nitrendipine group (ID 16.71). The risk reduction for eprosartan was 21% with confidence limits of 4% to 34% ($p = 0.014$). Separate analysis of the different components of the primary endpoint also revealed a superiority of eprosartan over nitrendipine in the total number of cerebrovascular events, including recurrent events (relative risk reduction of 25% with confidence limits between 3% and 42%; $p = 0.026$) and, although nonsignificant, in the total number of cardiovascular events, including recurrent events (relative risk reduction of 25%; $p = 0.061$).

In addition to the analysis of the total number of events occurred, MOSES investigators also analyzed the first occurrence of events in each category. There were no significant differences between eprosartan and nitrendipine in the first-time occurrence of cerebrovascular events and death from any cause, but, once more, eprosartan was superior to nitrendipine in the prevention of the first cardiovascular event (risk reduction of 31% with confidence limits between 3% and 50%; $p = 0.031$). This better protection was essentially due to fewer myocardial infarctions and new cases of heart failure.

Reasons for better cardiovascular protection in hypertensive stroke patients

Evidence-based medicine has demonstrated a superior effect of eprosartan over nitrendipine on cardiovascular protection. This is proven, although the explanation remains speculative. Some of the reasons for this superiority may be linked to a theoretical class effect of ARB, which have demonstrated a good profile in both the primary prevention of stroke and their impact on several risk factors that are clearly implicated in stroke development and recurrence (Sierra and de la Sierra 2005). However, before exploring these reasons, the effects of differences in BP or a negative effect of nitrendipine, which might also have influenced the results, should be ruled out. The MOSES investigators reported that the effect of two treatment regimens on BP values were essentially the same, as were the number of patients reaching BP goals at both 3 months of treatment and at the end of follow-up. Moreover, the number of patients receiving combination therapy and the median number of drugs in each group were also the same.

With respect to a possible negative effect of nitrendipine on cerebrovascular protection in patients with a previous stroke, there are no reports on the effect of calcium channel blockers on secondary stroke prevention. However, as mentioned above, recent meta-analyses of comparative trials of antihypertensive agents found a superior effect of calcium channel blockers on primary stroke prevention (Turnbull 2003; Angeli et al 2004), while nitrendipine was the basis of active treatment in patients with isolated systolic hypertension demonstrating a clear benefit on stroke prevention (Staessen et al 1997; Wang et al 2000). Thus, it would not be reasonable to suppose that a drug with a proven benefit on primary prevention would not have the same beneficial properties on secondary prevention of the same cardiovascular event.

The MOSES design was not able to completely rule-out a possible effect of the add-on therapy on the outcome. As this add-on therapy was left to the discretion of each investigator, the type of added medications was not identical between groups. In fact, although diuretics and beta-blockers were similarly distributed, more patients in the eprosartan group received other calcium channel blockers (14.4% versus 7.5% in the nitrendipine group) whereas ACE inhibitors were less frequently used (11.3% versus 21% in the nitrendipine group). Although it seems difficult to attribute to this imbalance an important role in the differences in cardiovascular protection observed in the MOSES trial, a contribution to the differences cannot be discarded.

ARB and stroke prevention

Three studies have compared ARB with other types of antihypertensive therapy in primary stroke prevention. The Losartan Intervention For Endpoint reduction (LIFE) study (Dahlöf et al 2002) compared losartan and atenolol in hypertensive patients older than 55 who had electrocardiographically detected left ventricular hypertrophy. Losartan significantly reduced the total number of cardiovascular events (13%) with minimal differences in BP changes between treatments. The benefit of losartan was mainly due to a decrease in the rate of stroke (25% reduction; $p = 0.001$).

The Study on Cognition and Prognosis in the Elderly (SCOPE) included hypertensive patients aged 70–89 who were randomly assigned to candesartan or placebo with open-label active antihypertensive treatment added as needed (Lithell et al 2003). The primary composite endpoint, a combination of cardiovascular death, stroke, and myocardial infarction was reduced by 10.9%, which did not reach statistical significance. Of all the components of the primary endpoint, only the reduction in non-fatal stroke (27.8%; 95% confidence interval [CI]: 1.3–47.2; $p = 0.04$) was statistically significant. However, there were marked differences in BP reduction (3.2/1.6 mmHg) between candesartan and placebo-treated patients.

Finally, the largest study with ARB in hypertensive patients was the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial. The VALUE trial (Julius et al 2004) compared two active antihypertensive treatments (valsartan and amlodipine) in high-risk hypertensives older than 50 years. At the end of the study there were no differences in the primary endpoint, which occurred in 10.6% of valsartan-treated patients and in 10.4% of amlodipine-treated patients. Some of the prespecified secondary endpoints were favourable to amlodipine with respect to valsartan, including myocardial infarction and stroke, whereas valsartan slightly reduced the development of heart failure.

The VALUE trial showed important differences in the BP reduction achieved by the two treatment regimens. Blood pressure differences were especially apparent during the first part of the study (4/2.1 mmHg in the first month) and were maintained at more than 1mmHg in favour of amlodipine during the entire follow-up.

Therefore, two of the three above-mentioned trials of ARB in hypertensive patients suggested a protective effect

of these drugs in the primary prevention of stroke. In fact, the cardiovascular protection observed in the LIFE trial was almost entirely due to stroke prevention. Moreover, although the primary-endpoint results of the SCOPE trial were not significant, the rate of non-fatal stroke was lower in the candesartan group. These results, combined with the MOSES results with eprosartan, suggest better cerebrovascular protection in hypertensive patients treated with ARB.

Another complementary evidence of a protective effect of ARB in cerebrovascular prevention comes from the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study (Schrader et al 2003). Hypertensive patients with an acute ischemic stroke were randomized to early candesartan or placebo, although all except two patients in the placebo group were then treated with candesartan 7 days after the stroke. Treatment was maintained during 12 months. The ACCESS trial demonstrated a beneficial effect of early candesartan on mortality (2.9% versus 7.2%; $p=0.07$) and in the number of vascular events (9.8% versus 18.7%; $p=0.026$), without significant differences in the level of BP between groups.

Possible mechanisms of cerebrovascular protection with ARB

Several different (and probably complementary) mechanisms have been proposed to explain the better cerebrovascular outcome in patients treated with ARB, including left ventricular hypertrophy regression, protection against atrial enlargement and supraventricular arrhythmias, effects on endothelial function, risk biomarkers and vascular remodelling, and a specific neuroprotection mediated through angiotensin II and the angiotensin II type 2 (AT_2) receptor.

In the LIFE trial, the cardiovascular protection observed was related to left ventricular hypertrophy regression (Devereux et al 2004; Okin et al 2004). Patients in whom both the Cornell product and Sokolow-Lyon voltage, (the electrocardiographic criteria used to define left ventricular hypertrophy), were reduced exhibited lower rates of the primary composite endpoint (strokes, myocardial infarctions and cardiovascular deaths). This included between 10% and 20% reduction in stroke rates (Okin et al 2004). Losartan-induced changes in these parameters were significantly more pronounced than those observed in atenolol-treated patients. These data have been confirmed in the substudy of LIFE in patients with left ventricular hypertrophy assessed by echocardiography. In this substudy, left ventricular mass regression was accompanied by a 24% risk reduction in the rate of stroke (Devereux et al 2004). This effect on the regression of left ventricular hypertrophy can also be linked to better protection against atrial fibrillation. Supraventricular arrhythmias are frequent in hypertensive patients with diastolic dysfunction related to the increase in ventricular mass, which promotes atrial enlargement. It is recognized that atrial fibrillation is one of the main risk factors for stroke, especially when accompanied by hypertension, older age, or left ventricular dysfunction. A post-hoc analysis of the LIFE trial revealed that rates of new onset atrial fibrillation were significantly reduced in losartan-treated patients compared with those who received atenolol (Wachtell et al 2005). This suggests a specific effect of this class of drugs on myocardium that is not dependent on BP. Moreover, experimental data show that ARB can have a direct effect on atrial electrical remodelling (Nakashima et al 2000). Although differences in new onset atrial fibrillation in the LIFE trial were too small to account for stroke differences, these effects of ARB on left ventricular hypertrophy regression and probably a better protection against arrhythmias represent advantages in terms of general cardiovascular protection, including stroke.

Endothelial dysfunction is one of the most important mechanisms involved in the development of atherosclerosis and is present in patients with various cardiovascular risk factors, including hypertension, hypercholesterolemia, and type 2 diabetes, as well as in patients with coronary artery disease. Endothelial dysfunction has important prognostic implications in these groups of patients (Schächinger et al 2000; Perticone et al 2001). Blocking RAS with ARB clearly ameliorates endothelial dysfunction, an effect that is not totally dependent on BP reduction. In an elegant study (Schiffrin et al 2000), resistance arteries obtained from gluteus subcutaneous biopsies from a small group of hypertensive patients and normotensive controls were studied by measuring the endothelium-dependent and independent responses and the cross-sectional area. Patients were then randomized to losartan or atenolol for one year and the procedures repeated. The results showed that patients treated with losartan normalized acetylcholine-dependent vasorelaxation and also reduced the ratio of the media/lumen diameter. No changes were observed in atenolol-treated patients despite a similar reduction in BP.

The effect of treatment on atherosclerosis biomarkers is closely linked to endothelial function. Several of these biomarkers, including acute-phase reactants such as C-reactive protein and adhesion molecules and selectins that

mediate vascular inflammation, have been implicated in the prognosis of patients at risk or those with cardiovascular diseases, especially coronary artery disease (Blankenberg et al 2001; Libby et al 2002). Various studies have shown an improvement in these parameters by blocking the effects of angiotensin II. Two months of candesartan therapy promoted reductions in oxidative stress (malondialdehyde), inflammatory biomarkers (monocyte chemotactic protein, tumor necrosis factor-α), and thrombotic factors (plasminogen activator inhibitor type-1) in 45 hypertensive patients independently of BP changes (Kon et al 2003). Moreover, C-reactive protein, interleukin-6, and monocyte chemotactic protein-1 (MCP-1) were reduced in patients after olmesartan treatment (Fliser et al 2004), while, in the only comparative study of eprosartan against hydrochlorothiazide (Rahman et al 2002), decreases in MCP-1, soluble vascular cell adhesion molecule-1 (sVCAM-1), and superoxide anion generation were only observed in patients treated with eprosartan despite similar BP reductions.

There is growing experimental evidence suggesting that some actions directly related to the stimulation of the AT_2 receptor may be involved in the cerebroprotection of ARB. Several angiotensin receptors mediate angiotensin II actions. Most of the deleterious effects of angiotensin II are mediated by the AT_1 receptor, which is selectively blocked by ARB. Conversely, stimulation of the AT_2 receptor by the same angiotensin II seems to promote vasodilation, natriuresis and apoptosis and impairs cellular hyperplasia (Fournier et al 2004). Some preliminary data support the idea that the AT_2 receptor is expressed more intensively in the brain than in the heart and that this expression is enhanced in patients with target organ damage, especially when cerebral ischemia occurs (De Gasparo et al 2000). In experimental models, AT_2 receptor stimulation protects brain tissue from ischemia (Li et al 2005). Treatment with ARB would increase angiotensin II concentration (Struck et al 2002), thus promoting the availability of this angiotensin II to bind the AT_2 receptor and to mediate the previously-mentioned beneficial actions. Other forms of RAS blockade, such as treatment with ACE inhibitors, would decrease angiotensin II and thus would not share the beneficial effects mediated through AT_2 receptor stimulation.

Eprosartan: an ARB with a dual mechanism of action

In addition to the RAS, the SNS seems to play an important role in the pathogenesis of essential hypertension, metabolic syndrome, and target organ damage related to elevated BP. Sympathoinhibitors, such as moxonidine, peripheral alpha-blockers, or beta-blockers have been widely used to treat high BP. In addition, it has been shown that blocking the RAS with ACE inhibitors or ARB decreases SNS activity in hypertensive and renal patients (Ligtenberg et al 1999; Struck et al 2002; Klein et al 2003). In fact, Struck et al (2002) have demonstrated a clear inhibition of SNS by valsartan, but not nitrendipine. These results may help to explain the BP-independent cardiovascular protective effects of the ARB.

Angiotensin II type 1 receptors located postjunctionally in the vascular bed promote vasoconstriction, whereas those located prejunctionally increase norepinephrine outflow to the junctional area, thus contributing to further vasoconstriction. Studies in animal models have also shown that ARB suppress angiotensin II-induced sympathetic outflow, with differences in affinity for AT_1 receptor sites evident between individual agents within this drug class (Ohlstein et al 1997; Balt et al 2001; Guimaraes et al 2001). The effect of eprosartan, candesartan, valsartan, and embusartan on presynaptically- and postsynaptically-located AT_1 receptors was investigated in the pithed rat model. Whereas the effect on postsynaptic receptors was dose-dependent for all ARB, the sympathoinhibitory potency was clearly superior for eprosartan compared with the other ARB (Balt et al 2001). Moreover, another study comparing eprosartan and losartan on both sympathoinhibitor and direct contractile responses in the canine pulmonary artery (Guimaraes et al 2001) found a parallel effect of both eprosartan and losartan on direct contractile responses induced by angiotensin II, whereas at the prejunctional level, while eprosartan antagonized the facilitatory effect on noradrenaline release at the same doses that were effective postjunctionally, losartan was ineffective even at concentrations 10 times higher than those used to block the receptor postjunctionally.

These results have been recently confirmed in humans. In a comparative study against valsartan, eprosartan significantly reduced several hemodynamic parameters obtained after adrenergic and noradrenergic stress (Arosio et al 2005).

Effects of eprosartan on vasculature

Eprosartan is able to reduce several markers of vascular pathology in both experimental animal models and humans. In stroke-prone spontaneously hypertensive rats (SHR-SP) fed with a high-fat, high-salt diet, low doses of eprosartan (30 mg/Kg/day) induced a significant decrease in myocardial proinflammatory chemokine MCP-1 expression (Behr et al

2004). This effect was accompanied by reduced morbidity and mortality. In a previous study by the same group, SHR-SP treated with higher doses of eprosartan (60 mg/Kg/day) showed no mortality at 18 weeks, whereas all those treated with vehicle died by week 9 (Barone et al 2001).

Studies performed in hypertensive patients have consistently shown a significant effect of eprosartan on several markers of vascular damage and dysfunction. In a non-comparative study of 30 hypertensive patients, eprosartan significantly reduced platelet activation and platelet calcium mobilization from baseline (Labios et al 2004). In two comparative studies against losartan (Makris et al 2004) or enalapril (Leu et al 2004), eprosartan favourably influenced several markers of coagulation/fibrinolysis (reduction in plasminogen activator inhibitor-1 [PAI-1] and increase in tissue plasminogen activator [tPA] antigen), platelet activation, and endothelial function. These effects were comparable between eprosartan and enalapril, but superior to losartan. Finally, as mentioned above, in a comparative study against hydrochlorothiazide, eprosartan significantly reduced superoxide generation, MCP-1 and VCAM-1, despite a similar BP reduction (Rahman et al 2001).

Clinical profile of eprosartan

The clinical efficacy of eprosartan has been evaluated in randomized trials. Eprosartan has been compared with ACE inhibitors and other ARB (for reviews see Plosker and Foster 2000; Robins and Scott 2005). In patients with mild-to-moderate hypertension, eprosartan has been demonstrated to be equally effective compared with enalapril (Elliott 1999; Ruilope et al 2001). However, in a study that included patients with severe hypertension, eprosartan was significantly more effective than enalapril in reducing systolic BP (−29.1 versus −21.1; $p < 0.05$) (Sega 1999). Moreover, in comparative studies against losartan (Garcia Puig et al 1999) or telmisartan (De Rosa et al 2004), no differences were observed in BP reduction.

Conclusion

The ARB eprosartan has been shown to be superior to the calcium channel blocker nitrendipine in preventing cardiovascular disease in hypertensive stroke patients. Angiotensin-receptor blockers are able to favourably affect left ventricular hypertrophy regression, endothelial function, and markers of vascular inflammation and remodelling, as well as exert beneficial actions on sympathetic nervous activity and on brain tissue through the stimulation of the AT_2 receptor. All these actions help to explain the better outcome observed in the comparison between eprosartan and nitrendipine in hypertensive stroke patients.

Disclosure

Dr de la Sierra has received honoraria from Solvay Pharmaceuticals for speaker's presentations.

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