Eprosartan And Cognitive Function

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Due to its high frequency and associated health risks, hypertension has become an important worldwide health challenge. In 2000, 26.4% of the world’s adult population had hypertension, a figure that is expected to rise to 29.2% by 2025. The overall prevalence in men and women is similar, but increases consistently with age worldwide.1,3

Midlife hypertension is one of the principal risk factors for cerebrovascular diseases; recent studies have indicated a relationship between hypertension and cognitive function. The possibility of antihypertensive therapy having beneficial effects on cognition has been a subject of research interest for some time. There is an active brain renin–angiotensin system (RAS) and angiotensin-converting enzyme (ACE) circulating angiotensin 2 and receptors AT1-AT4 that have all been found in the brain. Increased activity of the RAS and increased levels of ACE have also been associated with cognitive impairment. Animal and experimental data have shown that increases in RAS activity have an effect on the acetylcholine pathway, explaining why patients with activated RASs are at higher risk of developing cognitive impairment. Therefore identifying antihypertensive drugs that target the RAS are of particular interest for the preservation of cognitive function.

Therapeutic trials of antihypertensive therapy have long been associated with substantial reductions in the incidence of stroke, myocardial infarction and heart failure.4 Now recent studies have suggested that effective antihypertensive therapy may also reduce the progression of cognitive impairment. However, these results are still relatively limited.

Positive effects were reported in the Systolic Hypertension in Europe (Syst-EUR) study. Long-term results confirmed the benefit and safety of therapy with a dihydropyridine calcium channel blocker (CCB) in elderly patients with isolated systolic hypertension (ISH).5 The Perindopril protection against recurrent stroke study (PROGRESS)6 was one of the first secondary prevention studies to show that a combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril with the diuretic indapamide reduced blood pressure and significantly reduced the risk of recurrent ischemic stroke and intracerebral haemorrhage versus placebo. Whilst the Heart Outcome Prevention Evaluation (HOPE)7 trial also produced a positive result with ramipril.

In the Study on Cognition and Prognosis in the Elderly (SCOPE),8 a positive effect of an angiotensin type 1 receptor blocker (ARB) on cognitive function was suggested but did not reach statistical significance in the subgroup of elderly hypertensive people with mild cognitive impairment at baseline.9

However, no benefit was evident in the Medical Research Council’s (MRC) [10] and Systolic Hypertension in the Elderly Program (SHEP) studies.11 More recently, the HYVET-COG study also demonstrated no benefit of indapamide/perindopril compared with placebo on cognitive function in a cohort of elderly patients above the age of 80 years.12

Although positive results were demonstrated in the SYST-EUR, PROGRESS, HOPE and SCOPE trials, there was a lack of definitive results. Reasons for this have been identified; insufficient power to detect modest treatment effects and possible differential effects of the antihypertensive regimen under scrutiny.13 Discrimination between an independent effect to prevent deterioration of cognitive function and indirect consequences of a reduction in the risk of cerebrovascular disease is also a consideration.

A similar effect may have contributed to the significant reduction in cognitive decline associated with use ramipril compared with placebo in the HOPE study. Conversely, the Vascular Dementia project of the SYST-EUR study demonstrated a reduction in the incidence of dementia in the placebo group compared to patients treated with nitrendipine. In a subgroup analysis of the SCOPE study14 the indications of a beneficial effect of antihypertensive treatments on preservation of cognitive function have been supplemented by the findings of community based studies.15,16

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Moreover, several studies have documented a reduction in the development of cerebral white-matter hyperintensities with antihypertensive therapy.\textsuperscript{17,18} Evidence for such an effect also emerged from the PROGRESS study\textsuperscript{17} and may have been a harbinger of an effect on cognitive function independent of the reduction in recurrent stroke. Although individually most of these trials suggested the trend that antihypertensive treatment can be protective against cognitive decline, none is statistically significant. However, meta-analysis were powered adequately to confirm this trend.

Fast and effective treatment of hypertension can have significant beneficial effects on both the risk of stroke and future cognitive decline, making the development and use of ‘dual action’ therapeutic agents such as the angiotensin receptor blocker eprosartan very important for the health of affected patients. The antihypertensive efficacy of eprosartan has been established in controlled clinical trials.\textsuperscript{19} It has shown antihypertensive efficacy similar to that of the ACE inhibitors enalapril\textsuperscript{20} in patients with mild to moderate hypertension and has also exhibited efficacy in elderly patients with isolated systolic hypertension.\textsuperscript{21}

Eprosartan is an orally administered and highly selective non-peptide, non-tetrazole angiotensin type 1 (AT1) receptor antagonist that is approved in over 40 countries, including all European Union countries and the USA, for the treatment of patients with hypertension.

In the Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study, once-daily eprosartan 600-800mg reduced cerebrovascular and cardiovascular events in patients with a history of hypertension and previous stroke significantly more than the ‘gold standard’ calcium channel blocker nitrendipine.\textsuperscript{22,23}

The Observational Study on Cognitive Function And Systolic Blood Pressure Reduction (OSCAR) trial was an open-label trial designed to evaluate the impact of eprosartan-based therapy on cognitive function. Participants were above 50 years old, had newly diagnosed hypertension (systolic blood pressure of 140 mmHg or above) and were able to receive eprosartan 600 mg/day, either as a monotherapy or in combination with other therapeutic agents.\textsuperscript{24} This study provided opportunities to examine the influence of the ARB eprosartan on trends in cognitive performance in a large and broadly derived population of patients with high blood pressure (BP). The study found that eprosartan based therapy for an interval of 6 months was associated with overall improvement in the Mini-Mental State Examination (MMSE) score. MMSE is established as the preferred instrument for monitoring cognitive function in hypertension studies.\textsuperscript{25} It is routinely used as a screening tool for cognitive impairment and documents cognitive changes occurring over time.

OSCAR is at present the largest single source of data on the relation between hypertension therapy and cognitive status in an international population of hypertensive patients managed in routine primary care settings, using a far larger population that had been included in randomised trials. The acquired data indicates that a regimen based on eprosartan is safe and well tolerated in both sexes and that the use of eprosartan as sole or primary BP lowering medication was associated with an increase in the MMSE score in this large population of patients with hypertension. However, OSCAR is not a randomised controlled trial and therefore, cannot be used to infer causality.

The link between antihypertensive treatment and improvement in cognitive function has yet to be conclusively proved, and there is a still a growing consensus that possible effects of antihypertensive treatment on cognitive function should be an area of continuing scrutiny,\textsuperscript{26,27} but it is important for cardiologists treating individuals with hypertension to be aware that they should consider the mind as well as the heart when deciding on a suitable antihypertensive therapy for their patients.

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