

Reduction of dementia by calcium-antagonist-based antihypertensive treatment

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Aims The purpose of the vascular dementia project, set up in the framework of the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial, was to investigate whether antihypertensive drug treatment based on calcium-channel inhibitor as first step could reduce the incidence of dementia.

Methods and Results The study was run on non-demented patients, at least 60 years old, with isolated systolic hypertension. Treatment was initiated with nitrendipine (10–40 mg . day⁻¹) possibly associated with enalapril (5–20 mg . day⁻¹) and/or hydrochlorothiazide (12.5–25 mg . day⁻¹). Cognitive function was assessed by the Mini Mental State Examination. The diagnosis of dementia was based on the DSM-III-R criteria. The aetiology of dementia was established using either the Modified Ischaemic Score with brain imaging or the Hachinski score. Median follow-up was 2.0 years. By intention-to-treat, the incidence of dementia was reduced by 50% from 7.7 in the placebo group (n=1180) to 3.7 cases per 1000 patient-years

in the active treatment one (n=1238) (21 vs 11 patients, $P=0.05$). At the last available evaluation, systolic and diastolic blood pressure were 8.3 mmHg and 3.8 mmHg lower ($P<0.001$) in the active-treatment group.

Conclusion In older people with isolated systolic hypertension, antihypertensive treatment started with nitrendipine reduced the incidence of dementia. In the mechanism of dementia prevention a neuroprotective role of calcium-channel blockers may be suggested. Reversing alterations in calcium homeostasis may represent a new opportunity to prevent the development of Alzheimer's disease. This mechanism, associated to the antihypertensive action of calcium inhibitors, makes this class of drugs a logical candidate for future trials in the area of dementia prevention.

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Key Words: Dementia, systolic hypertension, antihypertensive treatment, calcium-channel blocker.

Introduction

Prevention of dementia is one of the most important Public Health challenges for the twenty-first century. Although hypertension is the most powerful risk factor for vascular dementia^[1], the placebo-controlled Systolic Hypertension in the Elderly Program (SHEP)^[2] failed to confirm the hypothesis that a diuretic-based antihypertensive treatment would protect against cognitive deterioration. The goal of the Syst-Eur vascular dementia project^[3] was to investigate whether antihypertensive treatment starting with the calcium-channel blocker nitrendipine could reduce the incidence of dementia in older patients with isolated systolic hypertension.

Methods

The protocols of the Syst-Eur trial and of the Dementia project were extensively described elsewhere^[4,3]. Eligible patients had to be non-demented, 60 years old or over, with a sitting systolic blood pressure of 160–219 mmHg and a diastolic blood pressure below 95 mmHg. After stratification by centre, sex and previous cardiovascular complications, the patients were randomized to double-blind treatment with active medication or placebo. Active treatment was initiated with nitrendipine (10–40 mg . day⁻¹) possibly associated with enalapril (5–20 mg . day⁻¹) and/or hydrochlorothiazide (12.5–25 mg . day⁻¹), or both drugs. Syst-Eur investigators could opt to take part in the Vascular Dementia project and then had to enrol all their patients. One hundred and six centres from 19 European countries participated in the project. Dementia screening and diagnosis relied on the Mini Mental State Examination (MMSE), the

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Table 1 Clinical features of the treatment groups at randomization

| Characteristic | Treatment group | |
|--|------------------|---------------------------|
| | Placebo (n=1180) | Active treatment (n=1238) |
| Mean (SD) age in years | 69.9 (6.2) | 69.9 (6.5) |
| Mean (SD) body-mass index in kg . m ⁻² | 27.0 (4.0) | 27.0 (4.2) |
| Mean (SD) sitting blood pressure in mmHg* | | |
| Systolic | 173.4 (10.1) | 173.5 (10.1) |
| Diastolic | 86.0 (5.7) | 86.1 (5.6) |
| Mean (SD) age when leaving school | 16.2 (4.4) | 16.4 (4.7) |
| Median MMSE score (range) | 29 (15–30) | 29 (18–30) |
| Number of patients with characteristics at randomization | | |
| Women | 767 (65.0%) | 822 (66.4%) |
| Previous antihypertensive medication | 476 (40.3%) | 467 (37.7%) |
| Cardiovascular complications | 337 (28.6%) | 340 (27.5%) |
| Atrial fibrillation | 44 (3.7%) | 46 (3.7%) |
| MMSE score equal to 30 | 350 (29.7%) | 360 (30.4%) |
| MMSE score of 23 or less | 23 (1.9%) | 24 (1.9%) |

*Average of six sitting measurements, i.e. two at three baseline visits 1 month apart.

DSM-III-R criteria, the Modified Ischaemic Score with brain imaging or the Hachinski score^[3].

Results

The Syst-Eur trial was completed after two years as it had achieved its primary end-point in terms of stroke reduction. Thus, the number of patients for the present analysis totalled 2418. At randomization, the patients of the placebo (n=1180) and the active-treatment (n=1238) groups had similar characteristics (Table 1).

There were 21 cases of dementia in the placebo group and 11 in the active-treatment group. The number of patient-years were 2737 and 2885, respectively. Active treatment reduced the rate of dementia by 50% (95% CI 0–76%) from 7.7 to 3.8 cases per 1000 patient-years ($P=0.05$). In the per protocol analysis, active treatment decreased the rate by 60% (95% CI 2–83%) from 6.6 to 2.7 cases per 1000 patient-years ($P=0.03$). Active treatment reduced the incidence of Alzheimer's disease (fifteen cases versus eight) as well as this of vascular or mixed dementia (six cases versus three).

At the last available measurement, sitting systolic and diastolic blood pressure had fallen ($P<0.001$) by a mean (SD) of 13.4 (16.2) mmHg and 2.6 (7.8) mmHg in the placebo group and by 21.7 (16.2) mmHg and 6.4 (8.3) mmHg in the active-treatment group. The between-group differences ($P<0.001$) were 8.3 mmHg systolic (95% CI 7.0–9.6 mmHg) and 3.8 mmHg diastolic (95% CI 3.2–4.5 mmHg) ($P<0.001$).

At the last visit, nitrendipine was given to 83% of the patients in the active group, and it was the only treatment taken by 60%; enalapril was given to 32% of the patients and hydrochlorothiazide to 15%.

Discussion

In the present study, antihypertensive treatment starting with the dihydropyridine calcium-channel blocker nitrendipine reduced the rate of dementia by 50%. The mechanism of the dementia prevention remains speculative. The primary hypothesis was that a reduction in blood pressure would protect against vascular dementia^[3]. The prevention of Alzheimer's disease (AD) was unexpected, although recent studies indicate that vascular factors, particularly hypertension, may play a role in the development of degenerative dementias as well as vascular dementia proper^[5]. However, the observation that antihypertensive treatment with a thiazide did not protect against cognitive impairment in the SHEP trial^[2] argues against the prevention of dementia simply by lowering the blood pressure. In vascular and degenerative dementias the calcium-channel blocker nimodipine, had a beneficial effect on the MMSE scores evolution compared with placebo^[6]. Thus, an additional or alternative explanation, albeit still unproven, could involve specific neuroprotection conferred by calcium-channel blockade^[7]. Some studies have proposed that the ageing brain loses its ability to regulate intracellular calcium, leading to a cascade of cellular impairments and, ultimately, cell death. The hypothesis of a possible central nervous action of nitrendipine is also supported by the observation that this drug crosses the blood-brain barrier. Nitrendipine-binding in the rat brain also occurs mainly at those sites which are primarily affected by Alzheimer's disease, such as the superficial cortex, thalamus and hippocampus, and not in areas with low synaptic density.

Alterations in calcium homeostasis may be strikingly involved in brain ageing and in the neuropathology of AD^[7]. Senile plaques contain the beta-amyloid peptide (A β) generated by the abnormal β and γ cleavage of the

amyloid protein precursor (APP). The neuronal toxicity of $A\beta$ could be partly due to an increased Ca^{2+} concentration associated with enhanced vulnerability to excitotoxic stimuli. In cultured neurons, both the direct neurotoxicity of $A\beta$ and the excitotoxic vulnerability were attenuated when the cells were incubated in a Ca^{2+} -deprived medium. Furthermore, a sustained increase in intracellular calcium level could partly induce a modification of intraneuronal microtubules and an increased phosphorylation of protein tau leading to the development of fibrillary tangles which are the second hallmark of AD.

Conclusion

Reversing alterations in calcium homeostasis may represent a new opportunity to prevent the development of AD. This mechanism associated with the antihypertensive action of calcium-antagonists makes this class of drugs a logical candidate for future trials in the area of dementia prevention.

References

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