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Does the Antihypertensive Therapy with Calcium-Channel blockers improve the cognitive function?: A review of evidences

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RESUMEN

Los bloqueantes de los canales de calcio (BCC) son un grupo de drogas con estructuras químicas heterogéneas, entre ellas verapamil, ditiazen y dihidropiridinas. Introducidas en la medicina clínica en el año de 1960, son drogas de prescripción frecuente en el tratamiento de los desordenes cardiovascular. Los bloqueantes de los canales de calcio son ampliamente utilizados en clínica en razón de que inducen vasodilatación arterial inhibiendo los canales voltaje dependientes del calcio del músculo cardiaco y del músculo liso vascular, modificando así la concentración de calcio intracelular fomentando de esa forma la relajación muscular. Hipertensión, diabetes, fibrilación auricular, demencia multiinfarto, enfermedad de alzehimer y la isquemia cerebral son algunas nuevas indicaciones en investigación para el uso de bloqueantes de los canales de calcio. De nuestra revisión se desprende que los efectos atribuidos a los BCC en la función cognitiva se ubican todavía en el terreno de la investigación. Trabajos futuros aportarán claridad sobre el tema.

Palabras Clave: Hipertensión arterial, Función cognitiva, Bloqueantes de los canales de calcio, Calcio antagonistas, Terapia antihipertensiva.

ABSTRACT

As a group, verapamil, diltiazem and dihydropyridines are commonly named calcium channel blockers. Introduced into clinical medicine in the 1960s, they are among the most frequently prescribed drugs for the treatment of cardiovascular diseases. All calcium channel blockers that have been approved for clinical use induce vasodilation and lowering blood pressure by inhibiting the voltage-dependent calcium channels in vascular smooth muscle at significantly lower concentrations than are required to interfere with the release of intracellular calcium or to block receptor-operated calcium channels. They relax arterial smooth muscle and have little or not effect on most venous beds and hence do not affect cardiac preload. In addition to their proved cardiovascular effects, preclinical and clinical evidence shows that calcium channel blockers may be useful in the treatment of diverse central nervous system disorders such as

cerebral ischemia, epilepsy, depression and dementia. Hypertension, diabetes, smoking and atrial fibrillation are well-recognized risk factors for stroke and multiinfarct dementia which may develop to the clinical diagnosis of dementia know as Alzheimer disease. An acquired deficit in memory function, problem solving orientation, and abstraction, decreases the capacity of an individual to function in an independent manner and are major components of diseases related to dementia. In this context, the use of calcium channel blockers to treat hypertensive patients and its relation to cognitive function is reviewed in an attempt for elucidate any positive or negative connection between high blood pressure, calcium channel blocker treatment and cognitive function.

Key Words: Arterial blood pressure, Cognitive function, Calcium–channel blockers, Antihypertensive therapy.

INTRODUCTION

Calcium channel blockers were introduced into clinical medicine in the 1960s and are among the most frequently used and prescribed drugs for the treatment and management of cardiovascular diseases (Freher et al., 1999). According to the common view, their mechanism of action is based on an inhibition of the smooth muscle L-type calcium current, thus decreasing intracellular calcium concentration and inducing smooth muscular relaxation (Dhein et al., 1999). These groups of drug have proved to be effective in patients with hypertension, angina pectoris and cardiac arrhythmias and they may be beneficial for some patients with migraine, preterm labor, esophageal spasm and bipolar disorders (Abernethy and Schwartz, 1999). The first clinically available calcium–channel blocker, namely verapamil, is a congener of papaverine. Many other calcium–channel blockers are now available and have a wide range of structures. The largest group, which includes amlodipine, fenoldipine, isradipine, nicardipine and nifedipine, is called dihydropyridines (Hoffman and Carruthers, 2000).

L – TYPE CALCIUM CHANNELS

Voltage–sensitive calcium channels belong to a family of homologous proteins that also includes channels for Na^+ and K^+. These channels contain domains of homologous sequence that are arranged in tandem within a single large subunit (Na^+ and Ca^{2+}) or multiple smaller subunits with homologous sequences (K^+ channels). These domains or subunits contain several hydrophobic regions that span the membrane and outline an internal pore (Schwartz et al., 1988). All calcium channel antagonists bind to the a_{1c} subunit of the L-type calcium channel, which is the main pore-forming unit of the channel. This subunit is associated with a disulfide-linked a_{2d} subunit and an intracellular b subunit (Abernethy and Schwartz, 1999).

Regulation of the L-type channels may differ in different types of cells. In cardiac myocites, for example, these channels are activated by catecholamines and other stimuli that activate adenylyl cyclase or cyclic adenosine monophosphate-dependent protein kinase (Tsien et al., 1972; Reuter and Scholz, 1977; Kameyama et al., 1985). On the other hand, in vascular and visceral smooth muscle beds, these stimuli can activate, inhibit or have no effect on L-type

calcium channels, depending on the experimental conditions (Mitra and Morad., 1985; Droogmans et al., 1987). Additionally, L-type calcium channels are also activated by endothelin (Goto et al., 1989), angiotensin II (Ohya and Sperelakis, 1991) and the a_1-adrenergic system (Nelson et al., 1988).

CLINICAL PHARMACOLOGY

Today, despite of the great number of calcium channel blockers synthesized, only nine of them are currently available for clinical use in the United States for the treatment of hypertension, angina pectoris and supraventricular arrhythmias. In this context, long-term treatment with calcium channel blockers is by oral administration. Only diltiazem, nicardipine and verapamil are available in intravenous formulations, and nimodipine is approved for short-term use in patients with subarachnoid hemorrhage (Abernethy and Schwartz, 1999).

Pharmacokinetics

Although the absorption of these agents is nearly complete after oral administration, their bioavailability is reduced, in some cases markedly, because of first-pass metabolism in the intestinal wall and liver (Kolars et al., 1992). All these drugs are metabolized to less active metabolites in the liver by oxidative pathways, predominantly by cytochrome P-450 CYP3A, and to a lesser extent by others isoenzymes which belongs to this superfamily (Pichard et al., 1990; Guengerich et al., 1991; Kroemer et al., 1993). The effects of these drugs are evident within 30 to 60 minutes of an oral dose. All these agents are bound to plasma proteins to a significant extent ranged between 70–99%; their elimination half-lives range from 1.3 to 5 hours. During repeated oral administration, bioavailability and half-life may increase because of saturation of hepatic metabolism. All calcium channel blockers with the exception of diltiazem and nifedipine, are administered as racemic mixtures, with one active and one inactive stereoisomer with respect to blockade of L-type calcium channels (Abernethy and Schwartz, 1988). Hepatic biotransformation of calcium channel blockers such as verapamil may be greater in women than men (Schwartz et al., 1994).

Pharmacodynamics

All calcium channel blockers that have been approved for clinical use induce vasodilation and lowering blood pressure. There are some differences in the relative potency as vasodilators among these drugs, with nifedipine been considered the most potent of the dihydropyridines, and verapamil, diltiazem and bepridil having less potency (Abernethy and Schwartz, 1999). Calcium channel blockers inhibit the voltage-dependent calcium channels in vascular smooth muscle at significantly lower concentrations than are required to interfere with the release of intracellular calcium or to block receptor-operated calcium channels. The calcium channel blockers relax arterial smooth muscle, but they have little effect on most venous beds and hence do not affect cardiac preload (Murad, 1996). All classes of calcium channel blockers depress sinus-node activity and slow atrioventricular conduction, yet only verapamil and diltiazem delay atrioventricular conduction or cause sinus-node depression at doses used clinically.

Additionally, all calcium channel blockers produce concentration-dependent decreases in myocardial contractility in vitro, but only verapamil and diltiazem do so in vivo (Abernethy and Schwartz, 1999), (table 1).

Table 1: Pharmacokinetic profile of L-type calcium channel blockers

	Verapamil	Diltiazem	Nifedipine	Amlodipine	Lacidipine	Nitrendipine	Felodipine
Oral absorption (%)	> 90	> 90	> 90	> 95	> 90	80–90	> 90
Bioavailability (%)	10–30	30–60	30–60	52–88	30–60	20	20
Binding to Plasma Protein (%)	> 90	> 90	> 90	99	> 90	> 90	99
t-max (hours)	1–2	1–2	1–2	6–12	1–3	1–2	2–4
Half life (hours)	3–7	3–6	2–3	35–50	8	8	11–16
Hepatic metabolism	+++	+++	+++	+++	+++	+++	+++
Active metabolites	Yes	Yes	Yes	No	No	?	Yes

CLINICAL USES AND SOME CONTROVERSIES OF CALCIUM CHANNEL BLOCKERS

Hypertension

Essential hypertension include a range of different phenotypes and results from genetic modifications and the interactions of various risk factors, comorbid diseases, and target organ damage which are frequently associated with cardiovascular damage or cerebrovascular and renal diseases (Kurchnir, 1999). A large number of clinical trials have demonstrated the benefits of antihypertensive therapy. Such trials indicate that the relative risks of stroke, coronary artery disease and congestive heart failure are decreased in a significant way using diuretics, b-blockers and calcium channel blockers as antihypertensive drugs treatment (Kurchnir, 1999). In a European Trial, treatment with nitrendipine decreased the death rate from myocardial infarction by 56%, fatal and nonfatal cardiovascular end-point by 31%, and stroke by 42% (Staessen et al., 1997). From the point of view of the large number of clinical trials, it is considered that protective effects against cardiovascular events are also exerted by other long-acting dihydropyridines (Gong et al., 1996; Hansson et al., 1998). As pointed out by Kuschnir (1999), the impact of calcium channel blockers on the cardiovascular system can be summarized as follows: a) favorable haemodynamic changes, which include increased diastolic and systolic function and improved peripheral circulation, both at rest and during exercise, and increased coronary flow reserve (through a vasodilator effect), b) regression of left ventricular hypertrophy and vascular hypertrophy (regression in cardiac and vascular remodeling), and c) potential antiatherogenic effects.

Renal protective effects

An increased attention has been focused on the importance of therapeutic interventions in addition to effective blood pressure control, aiming at renal protection. In this regard, calcium channel blockers are effective antihypertensive agents for treating hypertensive patients with chronic renal impairment, but they have not been studied as intensively as angiotensin converting enzyme inhibitors in relation to their ability to slow the progression of renal insufficiency independently of their blood pressure lowering effects. There are possible mechanisms other than reduction of intraglomerular capillary pressure whereby calcium antagonists could delay the progression of chronic renal failure, including reduction of renal hypertrophy, attenuation of the mitogenic effects of growth factors, reduction of the metabolic activity of remnant kidneys, and modulation of macromolecular traffic across and entrapment in the mesangium (Giacheli, 1999).

Diabetic hypertensive patient

Calcium channel blockers can be used to treat hypertension in patients with diabetes mellitus because they do not affect lipid nor glucose metabolism, or renal function (National High Blood Pressure Education Program Working Group, 1994). Angiotensin converting enzyme inhibitors slow the progression of diabetic nephropathy and recent trials have linked calcium channel blockers with adverse cardiovascular events in hypertensive patients with diabetes (Preston, 1999). It is worthy to mention that calcium channel blockers such as verapamil and diltiazem also decrease the excretion of albumin and other proteins, and apparently improve insulin sensitivity (Kaplan, 1998).

Atherosclerosis

Flekestein (Drugs Ther. Boletin 1994; Flekestein, 1990) pointed out the relationship between calcium and the arterial wall in the atherosclerotic process. He showed the presence of calcium deposits in a larger proportion in comparison with lipid deposition in using atherosclerotic tissue. He also found evidence of the relationship of these deposits with age and its contribution to the artheriosclerotic process (hardening of the arteries). This process occurs when calcium reacts with elastin. This is called ectopic calcium (Flekestein, 1990), because it is out of its natural place like bones and teeth but not in artery walls.

Considering these findings, Flekestein proposed the use of the calcium channels blockers to avoid calcium deposition in the arterial walls.

Use of calcium channel blockers and the risk of cancer

The hypothesis that calcium channel blockers may be carcinogenic has been pointed out by different authors (Horton, 1996; Pahor et al., 1996[a]; Pahor et al., 1996[b]; Hardell et al., 1996). One of the proposed mechanism is that calcium channel blockers inhibit the process called apoptosis, in which damaged cells are eliminated (Durham and Walton, 1986; Trump and Berezesky, 1995), while another point to the block of transmembranous calcium channels, which may cause an intracellular decrease of calcium content in certain tissues (Hardell et al., 1996). The possibility of increased risk of cancer induced by calcium channel blockers is

supported by the work of Pahor and coworkers (1996[b]), where they showed that from all participants who were taking these drugs, they found a 1.7-fold increased incidence of cancer after 4 years of follow-up. However, Olsen and colleagues found no evidences of a tumor-promoting effect induced by these drugs (Olsen et al., 1997). Although this study is similar in the follow-up period to that of Pahor et al (1996b), both are too brief to measure a carcinogenic effect, even if the drugs act as tumor promoters. Finally, the authors suggest that studies with longer follow-up periods are needed to clarify any potential carcinogenic effect associated to these drugs (Olsen et al., 1997).

UTILITIES AND CONTROVERSIES OF CALCIUM CHANNEL BLOCKERS USED TO TREAT HYPERTENSIVE PATIENTS AND ITS RELATION TO COGNITIVE FUNCTION

Controversy - History

In 1995, some retrospective reports, showed that certain patients treated with short-acting calcium antagonists were at increased risk for myocardial infarction and had a higher mortality rate compared with patients treated with other cardiovascular drugs (59). Subsequently reports attempted to establish a connection between calcium antagonists and disorders as diverse as malignancy, parkinsonism, cognitive dysfunction and suicide (60). However, several prospective studies have reported that calcium antagonists exert a beneficial effect on morbidity and mortality in a variety of cardiovascular disorders such as hypertension, ischemic heart disease after myocardial infarction, and congestive heart failure due to dilated cardiomyopathy (61).

Hypertension, aging and memory loss. Remarkable facts and use of calcium channel blockers

Hypertension is an important public health challenge not only in the United States but also around the world because of its high prevalence and the concomitant increase in the risk of cardiovascular/renal disease. As many as 43 million Americans have hypertension, which is defined as a systolic blood pressure (SBP) ž 140 mmHg and or a diastolic blood pressure (DBP) ž 90 mmHg and/or taking antihypertensive medications (Burt et al., 1995). Moreover, hypertension is the most important modifiable risk factor for coronary heart disease (the leading cause of death in the US population), stroke (the third leading cause of death), congestive heart failure, end-stage renal disease, and peripheral vascular disease (MacMahon et al., 1990; Kannel and Belanger, 1991; Klag et al., 1996; He and Whelton, 1999).

Prospective studies have repeatedly identified an increasing risk of cardiovascular disease, stroke, and renal insufficiency with progressively higher levels of both SBP and DBP (MacMahon et al., 1990; Kannel and Belanger, 1991; Klag et al., 1996; He and Whelton, 1999).

As long as we know, calcium channel blockers have at least 33 years history in the therapy of hypertension. However, their potential indications are not limited to cardiovascular diseases. Preclinical and clinical evidence is accumulating showing that calcium channel blockers may be

useful in the treatment of various disorders of the central nervous system (Schuurman and Traber, 1994).

Efficacy of calcium antagonists has been shown in animal models of epilepsy, cerebral ischemia, depression, and dementia (Scriabine et al., 1989; Czyrak et al., 1989; De Jonge et al., 1993). One report showed that brain aging is associated with a reduction or even the loss of various functions such as learning and memory capability, diurnal rhythms, social behavior, and sensorimotor functions. This was observed not only in humans but also in many animals' species including rodents (Schuurman et al., 1986). Attempts to improve one or more of these old age-related deficiencies by pharmacological treatments have not been successful until now. However, a number of animal studies suggest that the calcium channel blocker nimodipine may be a drug candidate in the treatment of some behavioral symptoms that occur during aging (Schuurman and Traber, 1994).

Thirty years ago "atherosclerosis" was almost synonymous with dementia, now "Alzheimer's disease" is (Hachinski and Munoz, 2000). Most definition of dementia requires that the patient be incapable of self-sufficiency. By that time it is too late to do anything except provide symptomatic treatment regardless of the etiology of the dementia. The cornerstone of all criteria of dementia is memory impairment. This criterion works very well for Alzheimer's disease, where memory loss is an early and constant feature, but it seldom helps in identifying individuals with cognitive impairment on a vascular bases (Hachinski and Munoz, 2000).

Hypertension, diabetes, smoking, and atrial fibrillation are well recognized risk factors for stroke and multiinfarct dementia, and also now it appears that they may be risk factors for dementia diagnosed clinically as Alzheimer's disease. Moreover, preliminary evidence suggests that treating hypertension may decrease or delay dementia (Hachinski and Munoz, 2000).

Cognitive impairment, or an acquired deficit in memory function, problem solving, orientation, and abstraction, diminishes an individual's capacity to function independently and is a major component of dementing disease (Colsher and Wallace, 1991; Launer et al., 1995).

As we mentioned above, elevated blood pressure is an established risk factor for stroke (MacMahon et al., 1990) and contributes to silent small-vessel disease and white-matter hyperintensities seen on neuroimaging (Miller, 1983; Erkinjuntti et al., 1993; Tatamichi et al., 1994), thus, these cerebral lesions have been associated with cognitive impairment in both clinical and population-based studies.

Taking into account the evidences that elevated blood pressure is also a risk factor for vascular dementia (Erkinjuntti et al., 1993), it might be expected that as long as blood pressure continues elevated, cognitive impairment in old age patients might be increased (Launer et al., 1995). The results from cross-sectional studies or clinic-based studies, with a relatively short follow-up period are mixed: some suggest that elevated blood pressure may impair cognitive function (Wilkie and Eisdorfer, 1971; Wallace et al., 1985; Sands and Meredith, 1992; Starr et al., 1993), while others fail to show a convincing relationship between blood pressure levels and

performance on cognitive tests (Wilkie et al., 1976; Farmer et al., 1987; Elias et al., 1989; Scherr et al., 1991).

In a report from Great Britain, cognitive function was prospectively assessed in a large sample of older adults randomized to diuretics, b blockers, or placebo treatments groups to investigate the relation between treatments of moderately raised blood pressure and cognition (Prince et al., 1996). The analysis of data does not provide any evidence for a cognitive benefit from antihypertensive treatment. Even restriction of the analysis to those subjects who had completed the study and remained on their randomized medication throughout (therefore, the treatment effect on systolic blood pressure was maximal), did not reveal any difference in cognitive outcome between the placebo and active treatment groups. However, this result did not prove that when hypertension is treated effectively, cognitive effects might not be achieved. Finally, the authors concluded that treatment of moderate hypertension with diuretics or β blockers was unlikely to influence, for better or worse, subsequent cognitive function (Prince et al., 1996).

In a 15-years longitudinal study of blood pressure and dementia, Skoog and co-workers examined a gerontological and geriatric population to investigate the relation between blood pressure and the development of dementia. Their conclusion was that there is an association between high blood pressure at age 70 and dementia which developed more than 9 years later, suggesting that antihypertensive treatment may have remarkably implications in the development of dementia and perhaps Alzheimer's disease. It is worthy to mention that in this study despite of the sample size (382 patients) which is considered small, the authors assumed that is representative of subjects surviving up to the age of 85, indicating that the finding could be generalized to the total population of 85-years-olds, which might not be the case.

In 1992, the first prospective clinical evidence of possible adverse cognitive effects related to a calcium channel blocker aroused (Skinner et al., 1992). In this study when the crossover data were ignored and results for the first drug treatment was considered alone, change in performance on both digit symbol and Buschke selective reminding tests were worse for nifedipine than for atenolol. However, the study has a very narrow window of conclusions because: a) their results apply only to nifedipine and atenolol and might not be generalizable to other calcium-channel or b-receptor antagonists and b) with the exception of the Buschke selective reminding test and the digit symbol test, other tests failed to show any significant difference between the two drugs.

The Honolulu-Asia Aging Study examined the relationship of blood pressure measured in midlife to cognitive function measured 25 years later in late life (Launer et al., 1995). They found that the risk for reduced cognitive function in very old men progressively increases with systolic blood pressure levels measured in midlife 25 ± 1.1 years prior to the measurement of cognitive function, suggesting that midlife systolic blood pressure is a significant predictor of reduced cognitive function in later life, and that early control of systolic blood pressure levels may reduce the risk for cognitive impairment in old age (Launer et al., 1995).

On the other hand, the Canadian Study of Health and Aging, a prospective study was undertaken to examine prospectively the association between the use of calcium channel blockers and others antihypertensive drugs and cognitive function (Maxwell et al., 1999). They analyzed data from 509 subjects and after some of the died and exclusion of others for different reasons the total number of subjects for analysis was reduced to 205, of which only 68 were under calcium channel blockers treatment, either as monotherapy or in combination with other antihypertensive drug. A decline of 10 in performance on the Modified Mini-Mental State (3MS) was considered clinically significant. The authors interpreted their results saying that older people taking calcium channel blockers were significantly more likely than those using other agents to experience cognitive decline and emphasized the need for further trials to examine the associations between calcium channel blockers use, blood pressure and cognitive impairment in elderly patients, a statement very cautious from the authors. However and in agreement with the analysis made by Dinsdale (1999), in this study the duration of treatment was short, the number of subjects was small, the variables analyzed were numerous and the confidence limits were wide, therefore, the question asked by Dinsdale (1999), of what might those associations be?, still remain unanswered.

CONCLUSION

Today, the main clinical indications for calcium channel blockers are in the therapy of angina and hypertension in which these drugs are considered highly effective (Opie et al., 2000), however, their effects on cognitive function still remain a big controversy. There are a general agreement of opinions concerning that additional randomized controlled trials are needed to clarify this issue. While we wait until the light inside the tunnel is turned on, physicians faced with the need to treat hypertension and others related cardiovascular disorders in elderly patients, and calcium channel blockers still and will play a remarkably important role in the management and prevention of complications of different cardiovascular diseases.

REFERENCES

1. Abernethy DR, Schwartz JB. Pharmacokinetics of calcium antagonists under development. Clin Pharmacokinet 1988; 15: 1-14.

2. Abernethy DR, Schwartz JB. Calcium-Antagonists Drugs. N Engl J Med. 1999; 341: 1447-1457.

3. Colsher PL, Walace RB. Epidemiologic considerations in studies of cognitive function in the elderly: methodology and nondementing acquired dysfunction. Epidemiol Rev. 1991; 13: 1-27.

4. Dhein S, Salameh A, Berkels R and Klaus W. Dual mode of action of dihydropyridine calcium antagonists: a role for nitric oxide. Drugs. 1999; 58 (3): 397-404.

5. Dinsdale HB. Searching for a link between calcium-channel blockers and cognitive function. CMAJ 1999; 161: 534-535.

6. Droogmans G, Declerck I, Casteels R. Effects of Adrenergic agonists on Ca2+-channel currents in single vascular smooth muscle cells. Pflugers Arch 1987; 409: 7-12.

7. Durham ACH, Walton JM. Calcium ions and the control of proliferation in normal and cancer cells. Biosci Rep. 1982; 2: 15-30.

8. Elias MF, Schultz NR, Robbins MA, Elias PK. A longitudinal study of neuropsychological performance by hypertensives and normotensives: a third measurement point. J Gerontol Psychol Sci. 1989; 44: P25-P28.

9. Erkinjuntti T, Hachinski V. Rethinking vascular dementia. Cerebrovasc Dis. 1993; 3: 3-23.

10. Farmer ME, White LR, Abbot RD, et al. Blood pressure and cognitive performance. Am J Epidemiol. 1987; 126: 1103-1114.

11. Flekestein A, et al. Experimental antiarteriosclerotic effects of calcium antagonist. J Clin Pharmacol 1990; 30: 151-154.

12. Flekestein A. History and prospect in calcium antagonist research. J Moll Cell Cardiol 1990; 22: 241-251.

13. Freher M, Challapalli S, Pinto JV, Schwartz J, Bonow RO and Gheorgiade M. Current status of calcium channel blockers in patients with cardiovascular disease. Curr. Probl. Cardiol. 1999; 24: 236-240.

14. Giacheli CM. Ectopic calcification. Gathering hard facts about soft tissue mineralization. Am J Pathol 1999; 153: 671-675.

15. Gong L, Zhang W, Zhu Y, et al. Shanghai trial of nifedipine in the elderly (STONE). J Hypertens. 1996; 14 (10): 1237-1245.

16. Goto K, Kasuya Y, Matsuki N, et al. Endothelin activates the dihydropyridine-sensitive, voltage-dependent Ca^{2+} channel in vascular smooth muscle. Proc Natl Acad Sci USA 1989; 86: 3915-3918.

17. Guengerich FP, Brain WR, Iwasaki M, Sari M-A, Baarnhielm C, Berntsson P. Oxidation of dihydropyridine calcium channel blockers and analogues by human liver cytochrome P-450 IIIA4. J Med Chem 1991; 34: 1838-1844.

18. Hansson I, Zanchetti A, Carruthers SG et al. Effects of intensive BP lowering and low dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet. 1998; 351: 1755-1762.

19. Hardell L, Axelson O, Fredrikson M. Antihypertensive drugs and risk of malignant diseases. Lancet 1996; 348: 542.

20. Horton R. Do calcium antagonists cause cancer? Lancet 1996; 348: 49.

21. Kameyama M, Hofmann F, Trautwein W. On the mechanism of b-adrenergic regulation of the Ca channel in the guinea-pig heart. Pflugers Arch 1985; 405: 285-293.

22. Kaplan NJ. Curve not burned off by HOT study (editorial). Lancet 1998; 351: 1748.

23. Kolars JC, Schmiedlin-Ren P, Schuetz JD, Fang C, Watkins PB, Identification of rifampin-inducible P450IIIA4 (CYP3A4) in humans small bowel enterocytes. J Clin Invest 1992; 90: 1871-1878.

24. Kroemer HK, Gautier J-C, Beaune P, Henderson C, Wolf CR, Eichelbaum M. Identification of P450 enzymes involved in metabolism of verapamil in humans. Naunyn Schmiedebergs Arch Oharmacol 1993; 348: 332-337.

25. Kuschnir E. Impact of Calcium Antagonists on the Cardiovascular System. Drugs. 1999; 57 (Suppl 1): 11-17.

26. Lacidipine once daily calcium antagonist for hypertension. Drugs Ther Boletin 1994; 32(18): 60-1.

27. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik R. The Association Between Midlife Blood Pressure Levels and Late-Life Cognitive Function. The Honolulu-Asia Aging Study. JAMA. 1995; 274: 1846-1851.

28. MacMahon S, Peto R, Cutler J, et al. Blood Pressure, stroke, and coronary heart disease, part 1: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet. 1990; 335: 765-774.

29. Maxwell CJ, Hogan DB, Elby EM. Calcium-channel blockers and cognitive function in elderly people: results from the Canadian Study of Health and Aging. CMAJ. 1999; 161: 501-506.

30. Miller VT. Lacunar stroke. Arch Neurol. 1983; 40: 129-134.

31. Mitra R, Morad M. Ca2+ and Ca2+-activated K+ currents in mammalian gastric smooth muscle cells. Science 1985; 229: 269-272.

32. Nelson MT, Stander NB, Brayden JE, Worley JF III. Noradrenaline contracts arteries by activating voltage-dependent calcium channels. Nature 1988; 336: 382-385.

33. Ohya Y, Sperelakis N. Involvement of a GTP-binding protein in stimulating action of angiotensin II on calcium channel in vascular smooth muscle. Circ Res 1991; 68: 763-771.

34. Olsen JH, Sorensen HT, Friis S, McLaughlin JK, Steffensen FH, Nielsen GL, Andersen M, Fraumeni JF and Olsen J Jr. Cancer Risk of Calcium Channel Blockers. Hypertension 1997; 29: 1091-1094.

35. Pahor M, Guralnik JM, Ferrucci L, Corti M-C, Salive ME, Cerhan JR, Wallace RB, Havlik RJ. Calcium-channel blockade and incidence of cancer in aged populations. Lancet 1996[b]; 348: 493-497.

36. Pahor M, Guralnik JM, Salive ME, Corti M-C, Carbonin P, Havlik RJ. Do calcium channel blockers increase the risk of cancer? Am J Hypertens 1996[a]; 9: 695-699.

37. Pichard L, Gillett G, Fabre I, et al. Identification of the rabbit and human cytochromes P-450 IIIA as the major enzymes involved in the N-demethylation of diltiazem. Drug Metab Dispos 1990; 18: 711-719.

38. Preston RA. Renoprotective Effects of Antihypertensive Drugs. Am J Hypertens 1999; 12:19S-32S.

39. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's treatment trial of hypertension in older adults. BMJ.1996; 312: 801-808.

40. Reuter H, Scholz H. The regulation of calcium conductance of cardiac muscle by adrenaline. J Physiol (Lond) 1977; 264: 49-62.

41. Sands LP, Meredith W. Intellectual functioning in late midlife. J Gerontol Psychol Sci. 1992; 47: P81-P84.

42. Scherr PA, Hebert LE, Smith LA, Evans DA. Relation of blood pressure to cognitive function in the elderly. Am J Epidemiol. 1991; 134: 1303-1315.

43. Schwartz JB, Capili H, Daugherty J. Aging of womwn alters S-verapamil pahamacokinetocs and Pharmacodynamics. Clin Pharmacol Ther 1994; 55: 509-517.

44. Schwartz A, McKenna E, Vaghy PL. Receptors for calcium antagonists. Am. J. Cardiol. 1988; 62: 3G-6G.

45. Skinner MH, Futterman A, Morrissette D, Thompson LW, Hoffman BB, Blaschke TF. Atenolol compared with nifedipine: effect on cognitive function and mood in elderly hypertensive patients. Ann Int Medicine. 1992; 116: 615-623.

46. Skoog I, Lernfelt B, Landahi S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Odén A, Svanborg A. 15-years longitudinal study of blood pressure and dementia. Lancet. 347: 1141-1145.

47. Staessen JA, Fagard R, Thijs L, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350: 757-764.

48. Starr JM, Whalley LJ, Inch S, Shering A. Blood pressure and cognitive function in healthy old people. J Am Geriatr Soc. 1993; 41: 753-756.

49. Tatamichi TK, Desmond DW, Stem Y, Pik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns and relationship to functional abilities. J Neurol Neurosurg Phychiatry. 1994; 57: 202-207.

50. Trump BF, Berezesky IK. Calcium-mediated cell injury and cell death. FASEB J. 1995; 9: 219-228.

51. Tsien RW, Giles W, Greengard P, Cyclic AMP mediates the effects of adrenaline on cardiac Purkinje fibers. Nat New Biol 1972; 240: 181-183.

52. Wallace RB, Lemke JH, Morris MC, Gooden-berger M, Kohuot F. Relationship of free-recall memory to hypertension in the elderly: the Iowa 65+ Rural Health Study. J Chronic Dis. 1985; 38: 475-481.

53. Wilkie F, Eisdorfer C, Nowlin JB, Memory and blood pressure in the aged. Exp Aging Res. 1976; 2: 3-16.

54. Wilkie F, Eisdorfer C. Intelligence and blood pressure in the aged. Science. 1971; 172: 959-962.