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THE INFLUENCE OF THE ANGIOTENSIN-CONVERTING ENZYME'SINHIBITORS IN THE PROPHYLAXIS OF ISCHEMIC CEREBROVASCULAR ACCIDENTS

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Abstract

The premises for realizing such complex therapies start with the cognition of the structural and functional particularities of the normal cerebral circulation; it is characterized by the cerebral hemodynamic autoregulation (achieved via neurogenic and humoral mechanisms, whose functioning depends on the vascular wall's normal structure and on a normal endothelial function), by the cerebral microcirculation integrity, an area where, in fact, the impact of the ischemic aggression on the cerebral parenchyma occurs (which, in turn, requires the integrity of the hematoencephalic barrier and a normal capillary endothelial function) and by the effects of the neurotransmitters and other local and systemic mediators have on the cells from the cerebral parenchyma

Key words: cerebral hemodynamic autoregulation, cerebral circulation

INTRODUTION

When treating patients with an ischemic cerebral disease, we must consider a series of pathological changes which occur, in the area of the cerebral microcirculation, in patients with risk factors, especiallyin the case of those with hypertension; these changes are intensely amplified when acute cerebral ischemia settles in (Vogel RA., 1999, Gibbons GH and Dzau VJ., 1994, Pearson TA et al, 2002, Strong JP et al, 1999, Libby P, 1996).

Three types of such injurious changes deserve closer examination: the endothelial dysfunction (the decreased activity of the endothelial NO synthase, the increased endothelin activity, the increased expression of the angiotensin II AT1 receptors, the increased ICAM-1 expression,(13-18) followed by the activation of the leukocyte adhesion, by the

prothrombotic transformation of the endothelium, determined by the increased expression of the tissular and PAI-1 factors, along with the decrease of the t-PA activity), the appearance of inflammatory lesions mediated by leukocytes and cytokines (which cause further damages to the vascular wall and alter the hematoencephalic barrier, to the cerebral tissue and increased flow resistance in the microcirculation) and the increased platelet aggregation (with the appearance of thrombosis in the microcirculation) (Glagov S et al, 1987, Hackett D et al, 1998, Engstrom G et al, 2002, Zwaka TP et al, 2001, Verma S et al, 2002, Pasceri V et al, 2001).

Finally, all these vascular changes, amplified by the installation of the acute cerebral ischemia, determine a series of pathological cellular events in the cerebral tissue which, in the end, lead to cellular death (initially through necrosis and afterwards by apoptosis) and cerebral stroke (Tiu C et al, 2003, Kubler W., 2003, Schwartz GG et al, 2001, Collins R et al, 2003).

Based on the knowledge of these evolutionary and ethiopathogenetic particularities of ischemic CVA, the studies of the last 10 to 15 years have allowed the development of certain therapeutic solutions, mainly of preventing CVA, which have a certain specificity for the arterial cerebral area, very close to, but not always identical (sometimes even substantially different) to the ones utilized in the coronary heart disease.(Lalouschek W et al, 2003, Carroll CA et al, 2003, Chapman N et al, 2004, Devereux RB et al, 2003).

MATERIAL AND METHOD

In order to complete it, we will select three groups of patients with minor cerebrovascular risk factors, patients with major cerebrovascular risk factors as well as patients who have already suffered an ischemic CVA

The endothelial dysfunction will be assessed by non-invasive methods like the intima-media thickness, the pulse wave velocity, the flow mediated vasodilatation, but also by biochemical markers.

The patients selected for the study will either be prescribed treatment with angiotensin-converting enzyme inhibitors or with inhibitors of the AT1 receptors, in doses adequate with the blood pressure values; we will track their effect on the endothelial dysfunction, as well as the incidence of the ischemic cerebrovascular accidents

RESULTS AND DISCUSSION

The clinical pharmacology studies have shown an increasing trend in the fibrinolytic activity, by lowering the PAI-1 level in the circulation of the

patients with hypertension, who were treated with perindopril,[42] as well as a preventive effect of perindopril[43,44] regarding atherosclerosis. Furthermore, the experimental studies which focused – via morphometric measurements – on the effect of the treatment with different doses of perindopril in subjects with both normal blood pressure and hypertension, on the hypertrophy changes and the vascular wall remodeling, have demonstrated that, for a usual antihypertensive dose, the vascular wall undergoes a normalization, both via an intervention on the parietal hypertrophy mechanisms, as well as on the vascular remodeling ones; the smaller dose does not influence hypertrophy and BP values have are less significantly decreased.

Clinical studies have shown an effect of great practical importance, namely that perindopril (and other ACE inhibitors, which do not decrease BP values suddenly) does not decrease the cerebral blood flow (measured by ultrasound), even though it decreases the systemic BP values, a trait which most usual antihypertensive medications lack.

The patients' characteristics, upon their inclusion in the study and at the end of it.

The beta-blockers used on the study group, were, according to the frequency the were used: perindopril in a dose of 50 mg / day, carvedilol at a dose of 25 mg / day and a dose of nebivolol 5 mg / day

Table 1

The diastolic blood pressure values, depending on the beta-blocker that was used

Beta-blocker type	**Average**	**Standard deviation**
perindopril	5,85	6,055
carvedilol	2,83	8,008
nebivolol	4,90	9,034

By correlating the laboratory and experimental data with those of the clinical trials which have demonstrated the significant efficacy of the ACE inhibitors in the primary and secondary prevention of CVA, whether or not the patients are hypertensive or have normotensive, we can state that such a particularity is determined by the fact that this class of drugs manages to maintain the cerebral blood flow, in patients with symptomatic cerebral ischemia, due to their normalization effects on the endothelial dysfunction

and via their intervention on hypertrophy and the vascular remodeling, beyond the blood pressure control.

CONCLUSIONS

In conclusion, as general rules of conduct regarding the patient with an ischemic CVA, the main pursued goals, after the emergency treatment period, focus on the reperfusion of the damaged cerebral area and on neuroprotection, are to realize, as soon and as correctly as possible (taking into account the etiopathogenic and clinical-evolutive particularities of each patient) an effective prophylaxis of another CVA, via an appropriate treatment that will achieve the vascular protection in the cervico-cerebral area, along with an antithrombotic treatment (antiaggregant or anticoagulant, where applicable) and/or surgery (endarterectomy or endovascular angioplasty), as well as a neuronal protection treatment that promotes neuroplasticity.

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