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NEUROPROTECTIVE BENEFITS OF ATORVASTATIN IN DEMENTIA AND STROKE

ATORVASTATİN'İN DEMANS VE FELÇ DURUMLARINDA SİNİR KORUYUCU YARARLARI

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Abstract

Dementia and stroke are the major health problem often occurs in older individuals aged 65 or more. There are many studies confirm that cholesterol might be involved in the pathogenesis of dementia and stroke. Atorvastatin, broadly used to lower cholesterol in coronary heart disease, are viable medications in decreasing the danger of dementia and stroke. Use of atorvastatin for prolonged period seems to be effective for the prevention of dementia and stroke. The objective of this review is to focuses the pharmacological benefit of atorvastatin in dementia and stroke.

Keywords: Dementia; Stroke; Atorvastatin

Özet

Demans ve felç 65 ya da daha yaşlı bireylerde sıkça görülen büyük bir sağlık problemidir. Kolesterolün demans ve felç patojeninizde yer aldığını doğrulayan pek çok çalışma vardır. Genel olarak koroner kalp hastalığında kolesterolü düşürmek için kullanılan Atorvastatin demans ve felç tehlikesini azaltmada uygulanabilir bir tedavidir. Atrovastatin'in uzun süreli kullanımının demans ve felci önlemede etkili olduğu görünmektedir. Bu çalışmanın amacı demans ve felç durumlarında atorvastatinin farmakolojik yararına odaklanmaktır.

Anahtar Kelimeler: *Demans; Felç; Atorvastatin*

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1. Introduction

Dementia is a most important public health problem because of its high occurrence in elderly individuals, mainly in the category of older subjects aged 65 or more (Barone et al., 2011). Dementia can be induced by a variety of conditions and the most common is Alzheimer's disease and in other clinical conditions, primarily or secondarily affecting the brain (Corrao et al., 2013). There is accumulating evidence that elevated serum cholesterol may be implicated in the pathogenesis of dementia.

Stroke is the rapidly raise the loss of brain functions due to a loss of blood flow in the brain. The Framingham Heart Study (FHS) and the Multiple Risk Factor Intervention Trial (MRFIT) confirmed a significant relationship between ischemic stroke and cholesterol levels (Kannel et al., 1971). High levels of cholesterol have decreased considerably after atorvastatin treatment in cerebrovascular disease. Atorvastatin is a lipid lowering agent; additionally it exerts an anti-inflammatory property which is important for prediction and treatment for dementia and stroke (Vijaya Anand et al., 2009). This review focuses the pharmacological benefit of atorvastatin on dementia and stroke.

2. Atorvastatin and Dementia

A group case control study based in the United Kingdom-based General Practice Research Database established that among the individuals with 50 years and older who taken atorvastatin therapy, the risk for developing dementia was considerably reduced, independent of their lipid status (Jick et al., 2000). In addition, there is no influence on the risk of developing dementia in this population who received other lipid-lowering agents. The systemic vascular protective effects of atorvastatin treatment are expected to add their beneficial effects, mainly on vascular forms of the dementia syndrome. Certainly, the results of the Heart Protection Study (HPS) and Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trials do not show the efficacy of statins in slowing cognitive refuse and dementia (Shepherd et al., 2002).

A de novo pharmacological effect of atorvastatin mediated by decreasing oxidative damage may be single mechanism which has the underlying benefits of atorvastatin in Alzheimer disease (Barone et al., 2011). Current evidence recommends that treatment of mild-to-moderate Alzheimer's disease with atorvastatin (80 mg/day) provide major benefit on the Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog) following 6 months. An important positive effect on ADAS-cog performance occurred, followed by 6 months of atorvastatin therapy compared with placebo, but the level of benefit produced may be predicated on prior treatment, a person's apolipoprotein E genotype or whether the patient shows high cholesterol levels (Sparks et al., 2006) .

Based on a population, group case-control trial was conducted with 152,729 patients from Lombardy (Italy) with 40 years of age or above who were recently treated with atorvastatin. Compared with patients who had a very low dose of statins coverage (less than 6 months), those of 7-24, 25-48 and>48 months of coverage correspondingly had a risk reduction of 15%, 28% and 25%. Simvastatin and atorvastatin were both related to a decreased risk of dementia, while no similar data was noted for fluvastatin and pravastatin. It is evident that the long-term use of atorvastatin seems efficient for the prevention of dementia (Corrao et al., 2013). Therefore, atorvastatin exert many positive effects through a variety of mechanisms in the presence of atherosclerotic risk factors.

3. Atorvastatin and Stroke

Large clinical trials with atorvastatin are the reduction in ischemic stroke (Crouse et al., 1998), for example, the HPS shows a 28% reduction in ischemic strokes in over 20,000 patients with cerebrovascular disease or other high-risk situation (Collins et al., 2004). As a result of the findings of these huge atorvastatin trials increase the interesting query of how a class of cholesterol-lowering agents can decrease ischemic stroke when the ischemic stroke is not associated with cholesterol levels.

Cerebrovascular tone and the flow of blood are regulated by endothelium-derived (nitric oxide) (Dalkara et al., 1994). Mutant mice lacking endothelial nitric oxide synthase (eNOS-/-) are fairly hypertensive and extend greater proliferative and inflammatory response to vascular injury (Huang et al., 1995). Certainly, eNOS-/-mice develop larger cerebral infarcts following cerebrovascular occlusion (Huang et al., 1996). Therefore, the valuable effects of atorvastatin in ischemic stroke may be due to their ability to up regulate the expression and activity of eNOS (Kureishi et al., 2000). Interestingly, statins treatment did not affect blood pressure or heart rate before, during and subsequent to cerebrovascular ischemia and did not modify levels of serum cholesterol in mice, consistent with neuroprotective properties of statins.

Additionally, to increase in cerebral blood flow, other beneficial effects of atorvastatin are possible to happen that can have a strong effect against on the severity of ischemic stroke. Atorvastatin lowers the P-selectin expression and leukocyte adhesion via increases in NO production in a model of cardiac ischemia and reperfusion (Lefer et al., 2001). Several other studies have reported that atorvastatin up regulate tissue-type tissue plasminogen activator (t-PA) and down regulate plasminogen activator inhibitor-1 (PAI-1) expression through a same mechanism involving inhibition of Rho (G-protein)

geranylation (Essig et al., 1998).

Early outcome measured by the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) was better in acute stroke patients treated with atorvastatin than in those treated with simvastatin. These variations may reveal a neuroprotective effect unique to atorvastatin (Lamp et al., 2010). The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial exhibit daily treatment with 80 mg of atorvastatin in patients with a recent stroke or TIA reduced the occurrence of fatal or nonfatal stroke by 16% (Huisa et al., 2010). Compared with placebo, use of high dose atorvastatin (80 mg/day) for secondary stroke prevention is not only of important clinical benefit but it is also low cost therapy. It produces major benefits in health with an incremental cost within reasonable limits (Arrospida et al., 2010).

Atorvastatin (20 mg/day) may be useful in reducing ischemic stroke frequency in ischemic stroke patients with a history of intracranial hemorrhage and is not associated with an increased risk of intracranial hemorrhage recurrence (Jia et al., 2013). Recently Ouk et al., 2013 study evidenced that the anti-inflammatory action of atorvastatin is arbitrated, by proliferator-activated receptor alpha (PPARα). The reduction in interleukin-6 (IL-6) plasmatic levels were PPARα dependent. The expression of the adhesion molecule intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) molecule was decreased by the atorvastatin treatment and this outcome was PPARα subordinate in the cortex, however not in the striatum of treated animals. Atorvastatin also decreased the cerebral expression of inducible nitric oxide synthase (iNOS) in the cortex, but there is no effect in the striatum of treated animals, whatever the PPARα status.

4. Conclusion

The most important result of this review is that atorvastatin is an effective lipid lowering drug. Treatment with atorvastatin provide a way of preventing the progression of dementia and stroke.

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