INTERNATIONAL JOURNAL OF
CLINICAL NEUROSCIENCES
AND MENTAL HEALTH

LECTURE

Should Vascular Dementia be treated with Cholinesterase Inhibitors?

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Special Issue on Controversies in Neurology. From the 10th World Congress on Controversies in Neurology (CONy), Lisbon, Portugal. 17–20 March 2016.

Abstract

Cholinesterase inhibitors are considered to be the first-line cognitive enhancer for Alzheimer's disease, but they do not have regulatory approval for treatment of vascular dementia in the United States and most of the Europe. There have been multiple studies of cholinesterase inhibitors in patients with vascular dementia over past decade. Cholinesterase inhibitors showed greater efficacy than placebo on ADAS-cog in some of these studies. However, these studies showed inconsistent benefit in global functioning of patients with vascular dementia.

Eisai's applications (Manufacturer of Aricept) for regulatory approval of donepezil for vascular dementia in 2002 and 2003 were rejected both in the United States and Europe. The development for this indication stopped. Donepezil has been studied frequently for patients with vascular dementia. One of the largest studies on donepezil, sponsored by the manufacturer, was a combined analysis using 2 identical randomized trial, 24-week period7. Patients were randomized to receive donepezil 5 mg/day or 10 mg/day, after brief titration or placebo. Both donepezil groups showed significant improvements in cognition compared with placebo (ADAS-cog, MMSE, $p < 0.01$). There was inconsistency in the global benefit. The 5 mg/day group showed benefit on the CIBIC-plus and the 10 mg/day group showed benefit on CDR-SB. The authors concluded that donepezil improved cognition, global function and ability to perform IADL in patients with vascular dementia and was well tolerated.

Kavirajan and Schneider did a meta-analysis of randomized controlled trials of cholinesterase inhibitors in vascular dementia from 1996-2006. Eight studies including the above double blind RCT studies comprising 5183 patients met their selection criteria. Their meta analysis attenuate the global effects of the 5 mg dose reported by published data. The Alzheimer's Disease Assessment scale was significantly improved for all drugs but only 5 mg daily donepezil had an effect on the Clinicians' Global Impression of Change scale. There was no behavioral or functional benefits on any of these drugs, except for 10 mg daily donepezil on the Alzheimer's disease Functional Assessment and Change Scale. They concluded that Cholinesterase inhibitors produce small benefits in cognitive abilities in vascular dementia but the clinical significance is uncertain.

As previous studies of Donepezil in vascular dementia showed inconsistent benefit in global functioning of patients with vascular dementia, the manufacturer sponsored another trial to further evaluate the potential benefits of donepezil in VaD. The participants were randomized only to donepezil 5 mg or placebo once daily. They achieved their previous results that patients treated with donepezil 5 mg/d had significant improvement in cognitive, but they did not show any improvement in global function.

A double-blind trial of Donepezil in patients with subcortical vascular cognitive impairment (CADASIL) failed to show any effect on the primary endpoint, which was change from baseline in the score on the vascular AD assessment scale

Citation: Tousi, B. Should Vascular Dementia be treated with Cholinesterase Inhibitors?. International Journal of Clinical Neurosciences and Mental Health 2016; 3(Suppl. 1):L14

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Published: 16 March 2016

cognitive subscale (V-ADAS-cog) at 18 weeks. Some improvements on few measures of executive function did not reach the clinical significance.

These initial studies used the now-outdated NINDS-AIREN criteria for probable VaD and the NINCDS-ADRDA4 criteria for possible AD, coupled with a requirement for radiological evidence of significant cerebrovascular disease for mixed dementia. Mixed dementia is now known to be very common. Both these criteria were prepared before this was recognized. When these criteria were prepared, small amounts of CVD were routinely ignored when seen in conjunction with what was otherwise thought to be AD. NINDS-AIREN criteria require an Alzheimer-like dementing process coupled with the presence of cerebrovascular disease. As such, these criteria are probably better criteria for mixed dementia than they are for VaD, There is some evidence from the both the galantamine and donepezil studies of a therapeutic effect for acetylcholinesterase inhibitors in VaD, or mixed AD and VaD, although in reality both studies are probably studies of mixed disease. When different sets of diagnostic criteria for Vascular dementia (ICD-10, DSM-IV and NINDS-AIRENS) have been compared against pathological findings as the gold standard, their sensitivity and specificity (in differentiating AD from VaD) are highly variable. These sets of criteria cannot be used interchangeably either. The overall design of efficacy trials in vascular dementia is questionable. A randomized, double-blind, placebo-controlled, parallel-arm design seems to be the most appropriate for AD with gradual worsening clinical course but a similar design may not be appropriate for vascular dementia. On current evidence, an acetylcholinesterase inhibitor could reasonably be considered for a patient with a spectrum of AD mixed with vascular disease. It is more important to emphasize the importance of early identification of cases with a vascular component to their cognitive decline, as these patients can benefit from prevention rather than just symptomatic treatment.

Since many patients with Vascular dementia also suffer from cardiovascular disease, a potential drug–drug interactions between cholinesterase inhibitor and the medications used to treat heart conditions in these patients is alarming. The potential inconsistent mild benefit of a cholinesterase inhibitor should be weighed against the harms likely to be caused to patients with vascular dementia.