

Vascular dementia: Pharmacological treatment approaches and perspectives

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Abstract: Vascular dementia is a common condition for which there are no effective approved pharmacological treatments available. Absence of effective treatments creates a difficult situation for those suffering from the disease, their caregivers, and healthcare providers. This review will address our current understanding of the mechanisms of nerve cell damage due to ischemia and summarize available clinical trial data on several commonly used compounds including memantine, donepezil, galantamine, rivastigmine, nimodipine, hydergine, nicergoline, CDP-choline, folic acid, as well as such nonpharmacological approaches as validation therapy.

Keywords: vascular dementia, excitotoxicity, treatment, NMDA, memantine, donepezil, galantamine, rivastigmine, nimodipine, hydergine, nicergoline, CDP-choline, folic acid

Introduction

Vascular dementia is a common condition. It has been estimated that 1 to 4 out of 100 individuals aged 65 years will develop it (Malouf and Birks 2004). The prevalence increases to 14–16 out of 100 individuals over 80 years old (Román 2002). Many individuals with vascular dementia will require institutionalization. Despite all of the recent investment in experimental and clinical neuroscience, there are no effective pharmacological compounds approved for treatment of vascular dementia in any jurisdiction worldwide. Such absence of effective treatments for a rather common disorder is uncommon in medicine and creates a difficult situation for those suffering from the disease, their caregivers and healthcare providers. For example, a number of studies have linked vascular dementia to mood disorders, particularly depression (Groves 1999; Lyketsos 2000) and greater caregiver burden was found among those caring for vascular dementia when compared with those caring for Alzheimer's disease (Vetter 1999; Annerstedt 2000). Urgent efforts are needed to address this knowledge vacuum. This review will discuss our current understanding of the mechanisms of nerve cell damage due to ischemia and will briefly summarize available vascular dementia treatment clinical trial data.

Clinical definitions and epidemiology

Vascular dementia represents a clinical syndrome that includes a wide spectrum of cognitive dysfunctions resulting from brain tissue death due to ischemia caused by vascular disease. A number of excellent reviews have been written on the topics of its diagnosis, pathogenesis, and epidemiology (Román 2002; Wallin 2003; Micieli 2006). It is believed that vascular dementia is a distinct clinical and pathological entity from Alzheimer's dementia, Lewy body dementia, or fronto-temporal dementia, although elements of vascular disease may be present in all of these conditions. Treatment of vascular dementia has also received extensive coverage (Broich 2003; Malouf and Birks 2004; Pantoni 2004; Schindler 2005). The prevailing conclusion of these reports is that most vascular dementia trials have produced disappointing results. It is important

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to note that so far no drug has been approved by regulatory agencies to treat vascular dementia (Pantoni 2004). Epidemiologically, vascular dementia is considered the second most prevalent type of dementia after Alzheimer's disease although this point of view maybe brought to doubt by our increasing understanding of Lewy body disease (Zesiewicz et al 2001; Henriksen et al 2006). From a clinician's point of view, vascular dementia represents a major source of frustration because of its relatively high prevalence and lack of effective treatment options.

Mechanisms of neurodegeneration and the role of glutamate receptors

Vascular dementia (VaD) arises as a consequence of ischemic insults such as hemorrhage and hypoperfusion that trigger neurodegeneration by depriving nerve cells of oxygen and glucose (Kalaria 2003; Francis 2006). Oxygen and glucose deprivation results in depletion of nerve cell energy supplies, leading to membrane depolarization, followed by an excessive release of glutamate, which, in turn, over activates the N-methyl-D-aspartate (NMDA) receptor/channel complex (NMDAR). Over activation of neuronal NMDA receptors allows influx of toxic levels of Ca^{2+} into nerve cells (Choi and Rothman 1990; Coyle and Puttfarcken 1993), which enables activation of various intracellular calcium-dependent enzymes (see Baskys and Blaabjerg, 2005 for review and refs. therein). The mechanism of glutamate toxicity and its various components are potential therapeutic targets, and merit a more detailed discussion here.

L-glutamate is a high affinity agonist on at least 4 major subtypes of neuronal glutamate receptors. Olney initially described glutamate toxicity in 1969 when he found that treatment of mice with monosodium glutamate caused brain lesions (Olney 1969). Three of these subtypes, named according to their preferred agonists kainate, AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA, implicated in cell death, are classified as ionotropic glutamate receptors (iGluRs), being directly linked to neuronal ion channels. It is generally believed that excessive stimulation of ionotropic glutamate receptors triggers an influx of Na^+ and Ca^{2+} through the receptor-controlled channels and subsequently leads to cell death. It has been proposed that Ca^{2+} entering through NMDA receptors may be especially lethal due to co-localization of these channels with particularly sensitive intracellular targets (eg, calpain-induced cytoskeletal breakdown, phospholipase-A2-induced formation of arachidonic acid and its metabolites, membrane translocation of protein kinase C, Ca^{2+} -activated endonuclease destruction

of cellular DNA, and other Ca^{2+} -dependent processes). For more details on the glutamate toxicity, the reader can be referred to several excellent reviews have been published on this topic (Portera-Cailliau et al 1997; Budd et al 1998; Martin et al 1998) recognizing the critical role of NMDA receptors in the pathophysiology of ischemic nerve cell death. The nature of cell death (necrosis vs. apoptosis) remains a subject of debate (as perhaps is the definition of the term "apoptosis" (eg, see Sloviter 2002). Morphological and other features of both apoptotic and necrotic cell death have been reported following ischemic damage (Nitatori 1995; Endres 1998; Francis 2006).

Based on this scenario it is not surprising that the focus in treating ischemic brain damage has been on designing drugs that are iGluR antagonists, in particular NMDAR antagonists (such as phencyclidine, ketamine or MK-801), and thereby inhibit the increase in intracellular Ca^{2+} . In animal models, these drugs have proved to be very effective against ischemic nerve cell injury, but in the human clinical trials the results have been disappointing, mainly due to severe side effects such as psychosis, nausea, vomiting, impaired memory and in some cases even cell death (Muir and Lees 1995). There have been numerous attempts to develop drugs that prevent ischemic brain tissue death, most of them unsuccessful. For example, out of 178 controlled clinical trials of acute stroke therapies reported in English language literature in the 20th century only four produced positive results. Among them, clot-dissolving treatments were more likely to be successful. In contrast, out of 49 neuroprotective drugs tested in 114 stroke studies none was successful (Gladstone 2002). The numerous reasons for this failure range from clinical trial design issues to failure to fully appreciate the complexity of regulations controlling nerve cell death and survival, and have received an excellent discussion elsewhere (Gladstone 2002).

Methods

An extensive search of Medline and the Cochrane database yielded slightly over twenty studies pertinent to this review. A wealth of information was found regarding treatment for Alzheimer's dementia, mixed dementia, and other types of cognitive impairment, but an attempt was made to focus exclusively on vascular dementia studies. Due to changing concepts of this disease over time, some older studies used diagnostic criteria different from current definitions. Efforts were made to use data appropriate to the current diagnostic definition of vascular dementia. In addition, some therapies (eg, folic acid, CDP-choline, validation therapy) were

included in this review due to their possible relevance to the treatment of vascular dementia, despite the lack of clinical trials specifically addressing the condition. A summary table was also prepared featuring results of selected trials focusing, again, on vascular dementia (Table 1).

Vascular dementia clinical trials

Memantine

Memantine belongs to the aminoadamantane chemical class and is structurally similar to amantadine, an antiparkinson and antiviral drug. It was initially developed to treat Parkinson's disease and was first tested in Europe in the 1990s, and later in the US, as a neuroprotective compound. In addition to its propensity to release dopamine from dopaminergic terminals, memantine is a weak, noncompetitive, open channel (use-dependent) antagonist of the glutamate NMDA receptor (Lipton 2004). Since NMDA receptor-mediated excitotoxic nerve cell death is considered of paramount importance in ischemic nerve cell damage, NMDA antagonist properties make memantine an attractive neuroprotective compound. On the other hand, NMDA receptor antagonists have been well known to cause hallucinations and impair cognition, attributes which have seriously hampered their clinical development.

Memantine has been tested in two studies that included 815 subjects with mild to moderately advanced vascular dementia (Areosa et al 2005, see Table 1). Treatment with 20 mg/day dose or placebo lasted 28 weeks. Data analysis showed a significant improvement in cognitive function, measured as ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale), from baseline, over placebo. There was no change in the CGI (Clinical Global Impression scale), CGIC (Clinical Global Impression of Change), or the NOSGER (Nurses Observational Scale for Geriatric Patients) self-care subscale. A small but statistically significant improvement was found on NOSGER disturbing behavior scale. In a study on a mixed patient population including Alzheimer's, vascular, and mixed dementia patients ($n = 168$), there was no significant effect on ADLs (Activities of Daily Living), but there was a significant positive effect on CGIC (Areosa 2005). No differences between memantine and placebo groups were found in dropout rates or the number of those suffering at least one adverse event, suggesting that the drug is well tolerated. Similar findings indicating an improvement in cognition and global function emerged from several smaller studies ($n = 59-88$) involving patients with unspecified dementia (Areosa 2005).

It appears from the above findings that memantine, an NMDA receptor antagonist, has a positive effect on cognition in patients with vascular dementia. This conclusion is in a very sharp contrast to the classical understanding of the NMDA receptor role in memory and learning (eg, see MacDonald et al 1996) and is difficult to explain. Lipton and Chen (2004) and Lipton (2004) proposed that memantine, which is an open channel (or use-dependent) antagonist of NMDA receptor channel, inhibits "elevated" NMDAR channel activity while leaving "normal" activity intact. This theory does not adequately address the fact that the clinical efficacy of memantine is significantly more pronounced in advanced dementia but not in early dementia where excessive NMDA receptor channel/activation would be the greatest. On the other hand, closed NMDA receptor channels do not appear to have any activity and it remains to be seen whether the proposed model is valid or memantine's clinical efficacy in dementia is mediated by a mechanism other than NMDAR channel blockade.

Galantamine

Galantamine is a cholinesterase inhibitor and n-cholino receptor modulator with documented efficacy in treatment of Alzheimer's disease symptoms. Two large studies involving vascular dementia patients were analyzed (Craig and Birks 2006). One included vascular dementia patients and Alzheimer's patients showing radiological and historical evidence of cerebrovascular disease. Analysis of the vascular subgroup showed that a galantamine effect on ADAS-cog did not reach statistical significance in comparison to placebo ($p = 0.06$). Analysis of all patients (combined vascular dementia and Alzheimer's with signs of cerebrovascular disease) showed a significant treatment effect on a variety of measures including ADAS-cog, CIBIC+ (Clinician's Interview-based Impression of Change plus caregiver input), NPI (Neuropsychiatric Inventory) and DAD (Disability Assessment for Dementia). There was a significant number of adverse effects in both analyses, which is in keeping with galantamine acetylcholinesterase inhibiting properties.

The second study that was analyzed included 786 subjects with vascular dementia (Craig and Birks 2006, see Table 1). One major change following 26-week galantamine treatment was in the ADAS-cog outcome measure. There was no difference in activities of daily living, global (CIBIC+) or behavioral (NPI) scales. Interestingly, there was a significant improvement in executive function. A similar improvement in executive function was also reported in a small double

Table 1 Summary of published meta-analysis data of vascular dementia treatment clinical trials

Treatment	Number of studies	Subjects	Duration	Benefit	Side effects	References
Memantine	2 studies Mild to moderate VaD	815	28 weeks	Improvement: Cognition (ADAS-cog) Behavior (NOSGER disturbing behavior scale) No change: Global rating (CGI, CIBIC-plus, CGIC) ADLs (NOSGER self-care)	No difference in those who had at least one adverse event	Areosa et al 2005 Orgogozo et al 2002 Wilcock et al 2002
Galantamine	1 study VaD + AD with cerebrovascular disease	449–543	24 weeks	Improvement: Cognition (ADAS-cog) Global rating (CIBIC-plus) Behavior (NPI) ADLs (ADCS-ADL)	Higher rates of withdrawals, withdrawals due to adverse event, total number of patients with at least one adverse event, and rates of nausea/vomiting. No difference in number of deaths	Craig and Birks 2006 Bullock et al 2004
	1 study VaD	786	26 weeks	Improvement: Cognition (ADAS-cog) Functional ability (DAD) No change: Global rating (CIBIC-plus) Behavior (NPI) ADLs (ADCS-ADL)	Higher rates of withdrawals due to adverse events No difference in incidence of adverse events or deaths through 30 days post-trial.	(GAL-INT-26, 2004 <i>unpublished data</i>)
Donepezil	2 studies VaD	1,219	12 weeks and 24 weeks	Improvement: Cognition (ADAS-cog, MMSE) Global rating (CIBIC-plus, CDR-SB) ADLs (IADLs, ADFACS)	Significant increase in one side effect or more No serious adverse effects	Malouf and Birks 2005
Rivastigmine	1 study VaD	16	22 months	Improved: Executive function (Ten point clock drawing) Behavior (NPI)		Moretti et al 2002
Hydergine	2 studies VaD 11 studies Various dementias	78 617	6 and 12 weeks 60 days to 12 months	No change: Global rating Improvement: Global rating Comprehensive rating	Not addressed No significant difference in at least one adverse effect	Olin et al 2002 and refs. therein Olin et al 2002 and refs. therein
Nicergoline	1 study Multi-infarct dementia	50	2 months	Improved: Global rating (CGI)		Fioravanti and Flicker 2001, Saletu et al 1995
	1 study Multi-infarct dementia	139	6 months	Improved: Memory (MMSE) Global rating (CGI)		Herrmann et al 1997
	1 study Alzheimer's dementia + Multi-	101	12 months	Improved: Memory (MMSE) Global rating (CGI)	No significant difference in at least one adverse	Fioravanti and Flicker 2001 and refs. therein

(Continued)

symptoms and has been approved by US Food and Drug Administration (FDA) for treatment of “idiopathic decline in mental capacity” (Olin et al 2006). Cochrane database search revealed meta-analysis results of 11 hydergine clinical trials on over 200 patients with diagnoses that included Alzheimer’s disease, vascular dementia, cerebral insufficiency and thromboembolic stroke. The combined analyses indicated that hydergine had statistically significant benefits on global measures in an apparent dose-dependent manner (see Table 1). However, greater effects were seen at doses higher than those currently approved by US FDA (>4.5 mg/day). The only two studies specifically looking at vascular dementia were quite small (n = 54, see Table 1) and analysis was limited because of the absence of comparable rating scales. Global rating changes were analyzed however, and found to be not statistically significant. Based on these analyses, clinical trial of hydergine at higher doses as well as more comprehensive investigations into its role in vascular dementia are needed to determine its potential clinical benefit.

Nicergoline

Nicergoline (8-beta-(bromonicotinoylhydroxymethyl)-1,6-dimethyl-10alpha-metoxerygoline) is another ergot derivative that has been in clinical use in over 50 countries for over three decades for treatment of cognitive, affective and behavioral disorders in older people. It has a multitude of effects that include actions on neurotransmitters such as acetylcholine, noradrenaline and dopamine, and intracellular signaling cascades. The Cochrane database provides meta-analysis data from 11 nicergoline clinical trials with approximately 1300 patients, half of who received nicergoline and the other half placebo (Fioravanti and Flicker 2004). Diagnoses of these trial patients varied, including “senile cognitive deterioration,” “cerebral metabolic and nutritional disturbances,” “hypertension and leukoaraiosis,” “senile cerebral insufficiency,” “senile dementia” and “senile dementia of Alzheimer’s type”. Two studies specifically dealt with patients diagnosed with “multi-infarct dementia” and another study focused on a population with multi-infarct dementia and Alzheimer’s type dementia (see Table 1).

Review of one mixed-group meta-analysis data revealed that there was a significant effect of nicergoline on MMSE scores in 261 patients from three studies ranging in duration from 3 to 12 months. The effect size obtained by using weighted mean difference and fixed effect model was 2.32 (95% CI 1.32–3.32) and was statistically significant. Two of the studies included patients with multi-infarct dementia.

No ADAS-cog data were found for patients other than those with the diagnosis of Alzheimer’s disease. On the CGI scale, mixed-group meta-analysis yielded a Peto odds ratio of 3.33 (95% CI 2.50–4.43) for improvement in subjects taking nicergoline as opposed to subjects taking placebo. Each of the three studies featuring patients with multi-infarct dementia also showed global improvement. Finally, for the mixed-group, there was a modest (Peto odds ratio 1.51) but statistically significant increase of adverse effects with nicergoline.

In summary, it appears that nicergoline may have a beneficial effect in vascular dementia but further studies with patients diagnosed using modern day diagnostic criteria are needed to confirm these findings. There are no data on the effects of the combination of acetylcholinesterase inhibitors or memantine with nicergoline in patients with vascular dementia.

Nimodipine

Nimodipine is an L-type voltage-dependent Ca^{2+} channel antagonist with antihypertensive properties. Excessive opening of voltage-dependent Ca^{2+} channels could accompany NMDA receptor-induced membrane depolarization and contribute to toxicity mediated by already large Ca^{2+} influx through NMDA receptor controlled ion channels. Therefore, blockade of these channels by nimodipine, could, at least in theory, lead to reduction of ischemic nerve cell death. Antihypertensive properties of Ca^{2+} channel blockade could further mitigate nerve cell damage in vascular dementia by eliminating an important risk factor (although blood pressure reduction did not substantially alter the course of vascular dementia, see below and Table 1). Review of the Cochrane database revealed meta-analysis data from 4 trials of nimodipine (90 mg/day at 12 and 24 weeks) in 409 patients with vascular dementia (Lopez-Arrieta and Birks 2005). These results were, unlike data with Alzheimer’s disease patients (presented in the same report by Lopez-Arieta and Birks 2005), disappointing. While there was evidence for statistically significant improvement of SCAG (Sandoz Clinical Assessment Geriatric) scores, global function, and cognitive function at 12 weeks, there was no statistically significant improvement in global function, cognitive scores, or CGI disease severity scores at 24 weeks. No improvement was seen in ADLs. These studies suggest that voltage-dependent Ca^{2+} channels play a limited, if any, role in pathogenesis of vascular dementia related symptoms and voltage-dependent Ca^{2+} channel antagonists such as nimodipine are not likely to be useful in their treatment.

Blood pressure-lowering therapies

It is an interesting question, both scientifically and clinically, whether eliminating one of the recognized risk factors for vascular dementia – elevated blood pressure—will reduce the incidence of vascular dementia. Three randomized, placebo-controlled studies involving over 12,000 patients with elevated blood pressure but no cognitive impairment examined whether lowering blood pressure would reduce the incidence of vascular dementia. Analysis of these studies revealed no convincing evidence that lowering blood pressure prevented development of cognitive impairment including vascular dementia (McGuinness et al 2006). Although quite convincing, these studies were not perfect in that the control group patients' blood pressures often exceeded preset allowable values, necessitating that the patients would have to receive antihypertensives.

CDP-choline

This compound is commonly used in European countries for treatment of cognitive disorders when their basis is thought to be vascular pathology. In ischemic conditions, CDP-choline (cytidine-5'-diphosphate choline; citicoline) is thought to act by blocking cell membrane degradation and release of toxic arachidonic acid and perhaps other harmful components of this process. It easily crosses blood-brain barrier. It is available as over-the-counter dietary supplement in the US and requires no prescription. There have been numerous studies of CDP-choline in various types of subjects, however, these studies vary significantly in their duration, subject selection, geography and outcome measures. Cochrane database is the source of several studies that included subjects whose complaints or diagnoses ranged from subjective memory complaints to moderately advanced vascular dementia (Fioravanti and Yanagi 2005). Available meta-analysis data indicate that treatment with CDP-choline results in a modest but statistically significant improvement in memory, behavior and global function (Fioravanti and Yanagi 2005). Clearly, additional studies with more uniform patient selection, accepted diagnostic criteria and outcome measures are needed to further understand CDP-choline benefits.

Folic acid

Folic acid is a vitamin which plays a key role in central nervous system development. Folic acid deficiency is associated with high homocysteine levels, which has been linked to an array of neuropsychiatric disorders, including depression and dementia and there has been much thought paid to the use of folic acid in improving cognitive function in the

elderly, especially in the case of dementia (Reynolds 2002). The Cochrane database provided meta-analysis data of four double-blind controlled trials with participants ranging from the healthy and cognitively intact, to mild-moderate cognitive decline, and to dementia (Malouf et al 2003). No benefit was found for improving cognition, though the trials were short (35 days to 3 months) and no specific subgroups of cognitive decline were studied. Further investigations with longer trials and focused examination of disease states such as vascular dementia may help to delineate the presumed benefits of folic acid in vascular dementia.

Validation therapy

Validation therapy is a collection of nonpharmacologic techniques described by Naomi Feil (1992) to treat disorientation and confusion in demented individuals. Empathy and consideration of emotional states are emphasized in relating to these patients. The therapy was examined for this review because of the recent attention paid to its legitimacy and efficacy. The Cochrane database revealed meta-analysis data from 3 small randomized trials of patients with dementia. There were no significant effects in terms of cognitive or behavioral benefit. However, one study did show behavioral improvements with validation versus placebo (see Table 1) and another found some benefit for depression with validation versus social contact (Neal and Wright 2006). Because of the low power of these studies, future investigations regarding the validation therapy may be useful in determining whether these positive results may be expanded upon.

Conclusions and future directions

From the studies reviewed here, one may draw several conclusions. First, there are relatively few studies on vascular dementia treatment and no compound has been approved by any regulatory body for treatment of vascular dementia. Second, it appears that there are several compounds with different mechanisms of action that show mild efficacy in improving cognition and even ADLs in patients with vascular dementia. Third, there is one compound (memantine) that has been suggested to act within the confines of the current excitotoxic cell death model, although direct evidence confirming this hypothesis is still lacking. Overall, one could easily conclude that a number of different mechanisms may be at play in etiopathogenesis of vascular dementia. Vascular conditions aside, nerve cell resistance to injury and our efforts to manipulate it still remains a conundrum, which will require new technologies to solve. One technology that might be particularly useful in this regard is microarray analysis of

messenger mRNA. Microarray analysis allows simultaneous monitoring of the behavior of a very large number of genes, up to the whole genome. Studies using microarray analysis reveal a very complex picture associated with the regulation of nerve cell susceptibility to injury (or other diseases such as cancer). For example, in a recent study of mechanisms that might be responsible for glutamate metabotropic receptor mediated neuroprotection against NMDA toxicity, cDNA microarray analysis of 1128 brain-relevant genes revealed that the neuroprotection was associated with simultaneous activation of endocytosis, and inactivation of inflammation, cell adhesion, apoptotic cell death, and transcription-related genes (Baskys and Blaabjerg 2005). This finding suggests that future neuroprotective drugs expected to be effective in treatment of vascular dementia will have to be directed simultaneously at multiple targets. Their components will have to be able to suppress inflammation, cell adhesion, apoptotic cell death and certain transcription-related genes to the extent that a pre-disease state could be achieved.

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