Pharmacologic interventions for vascular dementia

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Objectives

- Overview of vascular dementia
- Basis for pharmacologic interventions
- Review of the literature regarding pharmacologic interventions
Case – Mr. HR

- 83 yo man with cognitive impairment, family reports a stepwise decline in cognition over several years, memory impairment not prominent
  - MOCA 14/30, MMSE 23/30
  - P med hx: CVA 2009, MI 2000, HTN, DL, ex-smoker

- Is there a role for pharmacotherapy?
Vascular dementia includes a broad spectrum of disorders where cognitive dysfunction is due to brain tissue ischemia secondary to cerebrovascular disease

Second most common dementia type after Alzheimer’s

Variable definitions are used

- NINDS-AIREN criteria for probable vascular dementia
  - 1. dementia defined as a cognitive decline from prior higher level of function documented by clinical exam and neuropsychologic testing
  - 2. cerebrovascular disease defined as focal neurologic findings and relevant cerebrovascular changes on imaging
  - 3. temporal relationship defined as dementia within 3 months of a stroke or abrupt change in cognition or step-wise progression

Baskys 2007, Strokecenter.org
The risk factors for vascular dementia are similar to the risk factors for stroke, interventions that prevent recurrent cerebral infarction or slow atherosclerosis should improve the clinical course
- anti-hypertensives, aspirin, statins

Interventions that decrease oxidative stress may help to preserve cerebral tissue
- ginkgo biloba

Neurotrophic preparations may stimulate neuronal development or preserve existing tissues
- cerebrolysin

McGuinness 2009(a), Birks 2009, Plosker 2009
Patients with vascular dementia have lower choline acetyltransferase activity and CSF levels of acetylcholine compared to controls
- interventions that increase acetylcholine levels may provide some benefit to patients with vascular dementia
  - donepezil, galantamine, rivastigmine

Excessive intracellular glutamate activity may lead to increased cell damage during ischemic events,
- antagonism of the NMDA glutamate receptor may decrease this
  - memantine

Malouf 2009, McShane 2009
So what does the evidence show?*
Attempts were made to find higher levels of evidence
- NOT an inclusive list of the literature

Variable definitions of vascular dementia and some mixed trial populations

No outcomes used universally

Limited length of follow-up in most circumstances

Some data based on secondary and tertiary end-points
Cochrane review of prevention of dementia: 4 studies with effect of BP control on incidence of all types of dementia
- mean BP decrease 10/4 mm Hg
- incidence OR 0.89 (not significant)
- MMSE mean change 0.42

Cochrane review of Nimodipine: 209 patients with vascular dementia
- CGIC at 24 weeks: no difference

McGuinness 2009(a), Birks 2010
Aspirin

- Cochrane review: no trials were included

- Richards: 405 men randomized to ASA, ASA + warfarin, warfarin and placebo analyzed at 5 year follow-up
  - weschler test subsets and trailmaking not significantly different in patients taking vs. not taking ASA
    - ASA + ASA and Warfarin vs Warfarin + Placebo

Rands 2008, Richards 1997
Cochrane study of prevention: 2 studies with a total of 26,000 patients, both tertiary outcomes, statin vs. placebo
- incidence of dementia OR (HPS 2002): 1.00
- MMSE mean difference (PROSPER): 0.06

Cochrane study of treatment: 3 studies with a total of 704 patients with Alzheimer's dementia, statin vs. placebo
- ADAS-cog at 24-26 weeks: no difference
- CGIC: no difference

McGuinness 2009(b), McGuinness 2010
Ginkgo Biloba

Cochrane Review: 36 included studies, however variable end-points, many small trials, and mixed dementia population

- CGIC at 24-26 weeks: OR: 1.25 (NS, <200mg), 1.80 (≥200mg)
- ADAS-cog at 24-26 weeks: no difference at any dose

Birks 2009.
Cerebrolysin

- **Guekt:** 242 patients with vascular dementia, two 4 week courses of cerebrolysin plus ASA vs. placebo, with results at 24 weeks
  - ADAS-cog -10.6 vs -4.45
  - CIBIC-plus improvement 75% vs 37%

- **Xiao:** 147 patients with vascular dementia, 4 week course of cerebrolysin vs placebo
  - MMSE increase 2.7 vs 1.7
  - No difference in CGI

Guekt 2009, Xiao 1999
Cochrane review: 2 RCT’s with 1219 patients with probable or possible vascular dementia according to NINDS-AIREN criteria, 24 week F/U, donepezil vs. placebo

- ADAS-cog mean difference: -2.21 (10mg), -1.66 (5mg)
- CIBIC OR: 1.18 (10mg, NS), 1.56 (5mg)

Malouf 2009
Galantamine

- Cochrane review: 2 RCT’s identified
  - GALINT-6: Sub-group of 188 patients with vascular dementia, galantamine vs. placebo
    - ADAS-Cog mean difference: -2.29
    - CIBIC OR: 1.97
  - GALINT-26: 740 patients with vascular dementia, galantamine vs. placebo
    - ADAS-cog mean difference: -1.5
    - CIBIC not significantly different

Craig 2009(a)
Rivastigmine

- Cochrane review: No trials included

- Moretti 2003
  - 208 patients with CT evidence of ischemic changes and at least one lacunar infarct. 12 month open study of Rivastigmine vs. ASA.
    - BEHAVE-AD: -16.37 vs. +5.34
    - GDS: -3.9 vs +1
    - No significant difference in MMSE, clock drawing, word fluency

- Moretti 2004
  - 64 patients with probable vascular dementia, matched groups to rivastigmine 3-6mg or aspirin and nimodipine, 16 month open study
    - BEHAVE-AD: -16.9 vs. 5.2
    - GDS: -6.6 vs. 0.6
    - No significant difference in MMSE

Craig 2009(b), Moretti 2003, Moretti 2004,
Cochrane: pooled data from 2 studies, 900 patients with mild to moderate vascular dementia, 28 weeks duration
- ADAS-cog mean difference: 1.85
- CIGIC: no difference

McShane 2009
Summary

- Vascular risk factor control
  - Evidence that it is not effective in preventing or treating vascular dementia

- Ginkgo Biloba
  - Modest benefit, but studied in a mixed population

- Cerebrolysin
  - 2 studies in vascular dementia, mixed results

- Cholinesterase inhibitors
  - Donepezil and galantamine have shown modest benefits
  - Rivastigmine shows evidence for behavioural and mood improvement

- Memantine
  - Modest benefits
References

References

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