Calcium Antagonists for Aneurysmal Subarachnoid Hemorrhage

Sanne M. Dorhout Mees, MD; Gabriel J.E. Rinkel; Valery L. Feigin, MD, MSc, PhD; Ale Algra, MD; Walter M. van den Bergh, MD, PhD; Marinus Vermeulen, MD; Jan van Gijn, MD, FRCP, FRCP(E)

Secondary ischemia is a frequent cause of poor outcome in patients with subarachnoid hemorrhage (SAH). Its pathogenesis has been incompletely elucidated, but vasospasm probably is a contributing factor. Experimental studies have suggested that calcium antagonists can prevent or reverse vasospasm and have neuroprotective properties.

Objective
The objective of this study was to determine, in a systematic review of all randomized clinical trials (RCT), whether calcium antagonists improve outcome in patients with aneurysmal SAH.

Search Strategy
We aimed to include all RCTs on calcium antagonists in aneurysmal SAH. The Cochrane Stroke Group Trials Register (last searched April 2006), MEDLINE (1966 to March 2006), and EMBASE (1980 to March 2006) were searched. We hand searched 2 Russian journals (1990 to 2003), and contacted trialists and pharmaceutical companies in 1995 and 1996.

Selection Criteria
We included RCTs comparing calcium antagonists with control, or a second calcium antagonist (magnesium sulfate) versus control in addition to another calcium antagonist (nimodipine) in both the intervention and control groups.

Data Collection and Analysis
Two reviewers independently extracted the data and assessed trial quality. Trialists were contacted to obtain missing information.

Main Results
Sixteen trials (4 new since the previous review), involving 3361 patients, were included in the review; 3 trials studied magnesium sulfate in addition to nimodipine. In most included RCTs the aneurysms were treated by surgical clipping. Overall, calcium antagonists reduced the risk of poor outcome: the relative risk (RR) was 0.81 (95% confidence interval [CI] 0.72 to 0.92); the corresponding number of patients needed to treat was 19 (95% CI 1 to 51; Figure). For oral nimodipine alone the RR was 0.67 (95% CI 0.55 to 0.81), for other calcium antagonists or intravenous administration of nimodipine the results were not statistically significant. Calcium antagonists reduced the occurrence of secondary ischemia (RR: 0.66, 95% CI 0.59 to 0.75) and showed a favorable trend for case fatality. For magnesium in addition to standard treatment with nimodipine, the RR was 0.75 (95% CI 0.57 to 1.00) for poor outcome (Figure, bottom) and 0.66 (95% CI 0.45 to 0.96) for secondary ischemia.

Discussion
Calcium antagonists reduce the risk of poor outcome and secondary ischemia after aneurysmal SAH. The results for “poor outcome” depend largely on a single large trial of oral nimodipine; the evidence for other calcium antagonists is inconclusive. The evidence for nimodipine is not beyond all doubt, but given the potential benefits and modest risks of this treatment, oral nimodipine is currently indicated in patients with aneurysmal SAH. Intravenous administration of calcium antagonists cannot be recommended for routine practice on the basis of the present evidence. The aneurysms of most patients included in this review were treated by surgical clipping instead of endovascular coiling. Possible differences in effects of calcium antagonist on outcome between patients whose aneurysms are treated by coiling or clipping are not known. Magnesium sulfate is a promising agent, but more evidence is needed before definite conclusions can be drawn.

Implications for Clinical Practice
Based on the current evidence, the authors recommend oral nimodipine (60 mg every 4 hours, to be continued for 3
weeks) as standard treatment in patients with aneurysmal subarachnoid hemorrhage.

Note: The full text of this review is available in the Cochrane Library (for subscribers http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005951/frame.html).

Reference

Disclosures
None.
Calcium Antagonists for Aneurysmal Subarachnoid Hemorrhage
Sanne M. Dorhout Mees, Gabriel J.E. Rinkel, Valery L. Feigin, Ale Algra, Walter M. van den Bergh, Marinus Vermeulen and Jan van Gijn

Stroke. 2008;39:514-515; originally published online January 10, 2008;
doi: 10.1161/STROKEAHA.107.496802

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/2/514

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/