Calcium Antagonists in Aneurysmal Subarachnoid Hemorrhage

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Background
Secondary ischemia is a frequent cause of poor outcome in patients with subarachnoid hemorrhage (SAH). The cause of secondary ischemia is unknown, but may be related to vasospasm, at least in part. In experimental studies calcium antagonists prevent or reverse vasospasm and have neuroprotective properties. Various types of calcium antagonists have been studied in several clinical trials.

Objective
To determine the effectiveness of calcium antagonists for improving outcome in patients with aneurysmal SAH.

Methods
Search Strategy
We searched the Cochrane Stroke Group Trials Register (September 2003). In addition, we searched MEDLINE (1966 to October 2003) and EMBASE (1980 to October 2003), hand-searched two Russian journals (1990 to 2003), and contacted trialists and pharmaceutical companies (in 1995 and 1996) to identify further studies.

Selection Criteria
All randomized controlled trials comparing any calcium antagonist with control.

Data Collection and Analysis
Two reviewers independently extracted data and assessed trial quality. Trialists were contacted to obtain missing information. Primary analyses were based on the intention-to-treat results of the individual trials, for “poor outcome” (death or dependence), and for case fatality.

Results
We analyzed 12 trials totaling 2844 patients with SAH. The drugs analyzed were: nimodipine (8 trials), nicardipine (2 trials), AT877 (1 trial) and magnesium sulfate (1 trial).

Overall, calcium antagonists reduced the risk of poor outcome: the relative risk (RR) was 0.82 (95% confidence interval (CI), 0.72 to 0.93; Figure); the number of patients needed to treat (NNT) to prevent a single poor outcome event was 20 (95% CI, 12 to 59). For oral nimodipine alone the RR was 0.70 (0.58 to 0.84); the NNT was 8 patients (95% CI, 5 to 15). Results were inconclusive for nimodipine intravenously only (no data), nimodipine started intravenously and then orally (RR, 0.85; 95% CI, 0.57 to 1.28), for AT877 (RR, 0.84; 95% CI, 0.57 to 1.2), for nicardipine (RR, 0.97; 95% CI, 0.78 to 1.2), and for magnesium sulfate (RR, 0.70; 95% CI, 0.32 to 1.5). Results for nimodipine were no longer statistical significant when the largest trial was excluded from the analysis (RR, 0.83; 95% CI, 0.67 to 1.03).

The RR of death on treatment with calcium antagonists was 0.90 (95% CI, 0.76 to 1.07); RR of clinical signs of secondary ischemia was 0.67 (95% CI, 0.60 to 0.76), and RR of computed tomography– or magnetic resonance–confirmed infarction was 0.80 (95% CI, 0.71 to 0.89).

Conclusions
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 with oral nimodipine. The evidence for the effectiveness of nimodipine is not beyond doubt, but given the potential benefits and modest risks of this treatment, against the background of a devastating natural history, oral nimodipine (60 mg every 4 h) 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 evidence for nicardipine, AT877, and magnesium is inconclusive. Magnesium sulfate is a strong calcium antagonist, inexpensive, and readily available, and is therefore a
promising treatment in patients with SAH; but further trials are needed to study its effectiveness after aneurysmal SAH.


Key Words: aneurysm ▶ randomized controlled trial ▶ review ▶ subarachnoid hemorrhage