Calcium Antagonists: Stroke Therapy
Coming of Age

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While improved medical management may partially explain the impressive decline in mortality from stroke in the last three decades, clinicians have been limited in their ability to reduce the staggering neurologic morbidity in survivors. Many proposed interventions have had promising beginnings in the laboratory and have been employed with enthusiasm in uncontrolled series, but, sadly, none has withstood the test of randomized, controlled clinical trials. The recent FDA approval of the calcium antagonist, nimodipine (Nimotop, Miles Inc., West Haven, Connecticut), for treatment of ischemic complications in patients with aneurysmal subarachnoid hemorrhage (SAH) may herald a dramatic departure from this frustrating state of affairs. The data seem sufficiently promising to warrant optimism among investigators studying calcium antagonists for treatment of stroke and give hope that a new era may be dawning in which specific treatment for victims of ischemic injuries to the brain may be possible. The following represents an overview of calcium antagonists, the term preferred by the World Health Organization as opposed to calcium entry blockers or calcium channel blockers.\(^1\)

**Calcium Channels:**
**Molecular Biology and Physiology**

In neurons and muscle cells at rest, the intracellular free calcium concentration is maintained 10,000 times lower than in the extracellular space. Changes in free intracellular calcium concentration are critical in determining the multitude of responses of neurons and muscle cells to intracellular and extracellular stimuli. Continuous regulation of the transmembrane calcium concentration is required to maintain homeostasis so that these cells can detect small changes in free intracellular calcium concentration. Intracellular calcium homeostasis is regulated by three major interdependent systems: voltage dependent calcium channels (VDC), receptor or neurotransmitter operated calcium channels (ROC), and intrinsic mechanisms via intracellular second messengers (Figure 1). The distinction between ROC and VDC is not precise, since it is known that VDC can be modulated by ROC events, while ROC, including the N-methyl-D-aspartate (NMDA) type of glutamate receptor, can be influenced by voltage dependent events.\(^2\) The VDC are activated by cell membrane depolarization, which results in calcium influx. Three types of VDC have been identified in various tissues including smooth, skeletal, and myocardial muscle cells, neurons, glial cells, and endocrine secretory cells. Transient (T) and intermediate (N) VDC are insensitive to calcium antagonists, whereas long-lasting or slow (L) calcium channels are inactivated by calcium antagonists. There is a single-protein complex within or near each L-type VDC with at least four distinct recognition sites identified for the major calcium antagonist classes: the dihydropyridines, phenylalkylamines, benzothiazepines, and diphenylalkylamines.\(^3,4\) The binding sites for these four classes of calcium antagonists are functionally interdependent such that the binding of one class to L-type VDC may either inhibit or stimulate the binding of other calcium antagonists.\(^5\) The dihydropyridine receptor has been extensively studied, and its recognition sites have been successfully sequenced via molecular cloning.\(^6,7\)

**Pharmacology**

By binding to recognition sites, which results in conformational changes inactivating the L-type VDC, calcium antagonists restrict intracellular entry of calcium via VDC. At higher concentrations calcium antagonists also inhibit calcium entry via ROC. Thus, at pharmacologic doses calcium antagonists are potent relaxers of vascular smooth muscle, resulting in vasodilation. The "cerebroselective" calcium antagonists have preferential effects on calcium channels located in smooth muscle of cerebral blood vessels rather than peripheral blood vessels and myocardial cells. They are also highly lipophilic and can cross the blood-brain barrier, which results in higher cerebral concentrations. Cerebroselective calcium antagonists currently being investigated for treatment of stroke include the dihydropyridines—nimodipine, nicardipine, nilvadipine, PY 108-068, and PN 200-110, and the diphenylalkylamines—flunarizine and cinnarizine. These agents have potent vasodilatory effects on cerebral vessels with resulting...
increased cerebral blood flow, which led to investigation of their use in the treatment of ischemia due to cerebral vasospasm in SAH and in nonhemorrhagic cerebral infarction.8,9

Excess neuronal calcium entry via VDC, excitatory amino acid stimulated ROC, and nonspecific membrane leakage may be the critical factor in determining irreversible neuronal death in the setting of an ischemic insult. Increased free intracellular neuronal calcium due to disruption of calcium homeostatic mechanisms leads to depletion of high energy phosphates and activation of phospholipases and proteases and degradation of the neuronal cell membrane and production of cytotoxic free radicals, leukotrienes, and prostaglandins (Figure 1). Increased free intracellular calcium also causes uncoupling of oxidative phosphorylation and inhibits cellular respiration, leading to irreversible cell dysfunction and subsequent neuronal death. By limiting excess neuronal calcium entry via L-type VDC and probably also ROC during states of decreased cerebral perfusion, calcium antagonists may confer a neuronal protective effect which could prevent cerebral infarction following an ischemic insult, or they could limit the extent of infarction with reduction of neurologic disability. In contrast, experimental NMDA receptor antagonists, such as MK-801 and AP5, may exert a neuronal protective effect by inhibiting calcium influx via ROC.10

There may be other significant pharmacologic actions of the calcium antagonists that ameliorate the effects of cerebral ischemia. Calcium antagonists may

Figure 1. Top panel: Schematic representation of a neuron with normal calcium (Ca\textsuperscript{2+}) homeostasis: entry of calcium via voltage dependent calcium channels (VDC) and receptor operated calcium channels (ROC); uptake of calcium in mitochondria, endoplasmic reticulum and by binding proteins; and extrusion by ATP-dependent processes and in exchange for sodium (Na\textsuperscript{+}). Bottom panel: Schematic representation of an ischemic neuron: excess entry of calcium via VDC, ROC, and nonspecific membrane leakage, resulting in degradation of the cell membrane, production of cytotoxic free radicals and metabolites of arachidonic acid, uncoupling of oxidative phosphorylation, and inhibition of cellular respiration, as well as failure of mechanisms for extrusion of calcium.
decrease erythrocyte rigidity and improve blood fluidity. Several calcium antagonists have platelet antiaggregating effects, possibly through inhibition of calcium mediated platelet activation and by stimulation of vascular prostacyclin release, but this remains controversial and of undetermined significance. Calcium antagonists also inhibit mitogenesis of vascular smooth muscle cells and thereby inhibit experimental atherosclerosis in animals.

**Pharmacokinetics**

Most calcium antagonists are well absorbed in the gastrointestinal tract. However, with oral administration there is extensive first-pass hepatic metabolism that may reduce effective plasma concentrations and result in large interpatient and intrapatient variation in blood levels. Also, the bioavailability of orally administered calcium antagonists may be reduced when given after meals. These potential limitations may be avoided by intravenous administration. After the calcium antagonists are metabolized in the liver by saturable enzymatic processes, the metabolites are eliminated via the hepatobiliary and renal systems. The half-life of intravenous nicardipine is 4.75 hours, and mean plasma clearance is 8.2 ml/min/kg. For nimodipine the elimination half-life is 0.9–1.5 hours when administered intravenously and varies from 1.7 to 7.2 hours when given orally. Plasma clearance of calcium antagonists is prolonged at least two to threefold in the presence of hepatic or renal disease. The plasma concentrations of calcium antagonists are reduced with chronic anticonvulsant use, probably because of the induction of the hepatic mixed function oxidase system.

**Adverse Effects and Toxicity**

The potential adverse side effects and toxicity of calcium antagonists are most commonly related to their effect on smooth muscle of peripheral blood vessels and myocardium. Hypotension has been reported with an incidence of 4.7–8% in patients with SAH receiving nimodipine. Other cardiovascular effects include cardiac arrhythmias and negative inotropic effects, myocardial ischemia, vascular headaches, and facial flushing. Thrombophlebitis at peripheral intravenous sites can occur. Gastrointestinal side effects include transient abnormalities in liver function tests along with nausea, anorexia, diarrhea, constipation, and a single report of acute painful pseudo-obstruction of the colon. Reversible renal dysfunction has been noted with elevation of blood urea nitrogen and creatinine. Hypersensitivity reactions including skin rashes have been reported. Psychosis, drowsiness, dizziness, insomnia, and fatigue have also been rarely associated with use of calcium antagonists.

**Experimental Studies in Cerebral Ischemia**

A potential role for calcium antagonists in the treatment of cerebral vasospasm associated with aneurysmal SAH was initially proposed after numerous animal studies had demonstrated the ability of calcium antagonists to prevent experimental cerebral vasoconstriction induced by various agents, such as serotonin, phenylephrine, potassium chloride, carboxylic thromboxane A2, ATP, and caffeine. As a result of the cerebral vasodilator effect of calcium antagonists, increased regional cerebral blood flow and increased cerebral venous outflow were demonstrated in animals. Subsequent studies in dogs showed that calcium antagonists were effective in preventing and reversing SAH-induced acute vasospasm. However, oral or intravenously administered calcium antagonists were not effective in preventing reduction of vessel lumen diameter as a result of delayed cerebral vasospasm in dog and primate SAH models, which more closely approximate the human condition. Since these studies used angiography to assess vessel lumen diameter, they did not exclude the possibility that the calcium antagonists might be effective on small cerebral arteries in which they are known to have dramatic vasodilatory effects.

In animal studies with experimental focal cerebral ischemia, treatment with calcium antagonists has clearly demonstrated a beneficial neuronal protective effect by reducing calcium entry into ischemic cells while also preserving high energy phosphates, reducing abnormal electrolyte shifts of sodium and potassium, preventing local acidosis, and limiting development of cerebral edema. However, whether there is a beneficial effect of calcium antagonists on neuropathologic and cerebral blood flow variables following experimental focal cerebral ischemia is controversial. Gotch found reduction in the size of cerebral infarction and increased cerebral blood flow in rats only when calcium antagonists were administered before experimental focal ischemia but not when treatment was initiated after the ischemic insult. Subsequently, Germano demonstrated reduction of cerebral infarction and improved neurologic outcome when calcium antagonists were administered in rats after middle cerebral artery occlusion. Marcoux has also observed decreased volume of cerebral infarction in rats when calcium antagonists were given after combined middle cerebral and ipsilateral carotid artery occlusion. Sauter has shown that treatment with calcium antagonists in rats following middle cerebral artery occlusion resulted in decreased size of cerebral infarction as determined by magnetic resonance imaging and histopathologic examination.

Calcium antagonists have also been shown to have beneficial effects in global cerebral ischemia models with prevention of postischemic hypoperfusion and improved EEG activity. When compared with controls, improved neuronal somatosensory evoked responses were demonstrated in rats treated with nicardipine before and after being subjected to global cerebral ischemia. Calcium antagonists in a global cerebral ischemia rabbit model were associated with improved EEG recovery. In this model excess neu-
neuronal calcium influx and increased blood-brain barrier permeability were both limited by calcium antagonists. In a complete cerebral ischemia model with dogs, calcium antagonists improved cerebral blood flow following reperfusion, but neurologic outcome was improved only when calcium antagonists were administered prior to ischemia. However, in a subsequent study in primates with a different method used to induce complete cerebral ischemia, improved neurologic recovery and reduction in pathologic damage were seen when calcium antagonists were given in the postischemic period.

It is difficult to determine why calcium antagonists are of benefit in some experimental studies of focal and global cerebral ischemia but are not effective in others. Numerous factors may affect the results, such as dosage, duration and time of initiation of the calcium antagonists after ischemia, interspecies variation in responses, and differences in the models of cerebral ischemia.

Clinical Studies

Aneurysmal SAH

Cerebral vasospasm is the leading cause of mortality and neurologic disability in patients who survive the initial aneurysmal SAH. The incidence of angiographic vasospasm has been reported to be as high as 70% with 20–30% developing clinical ischemic symptoms (symptomatic vasospasm), while 14% die or are permanently disabled.

The use of oral nimodipine for vasospasm associated with aneurysmal SAH in patients in good neurologic condition (Hunt and Hess grades I–III) has been approved primarily on the basis of the results of five prospective, randomized, double-blind, placebo-controlled clinical trials (see Table 1). Allen et al reported that although there were no differences in overall neurologic outcome and rates of symptomatic vasospasm in the nimodipine and placebo groups, severity of permanent neurologic deficits due to cerebral vasospasm decreased significantly in patients receiving nimodipine. Philippon et al were unable to determine if there was improvement in overall outcome in patients receiving nimodipine, but again there were improved outcomes in the treated patients with symptomatic vasospasm. Neil-Dwyer et al reported an 83% reduction in mortality and 50% decrease in poor outcome in SAH patients treated with oral and intraoperative intracisternal nimodipine. In the Petruk et al study, which was limited to poor neurologic grade patients (Hunt and Hess grades III–V), there was an overall 7% reduction of poor outcome in patients treated with nimodipine. Also, there was a significant increase in good recovery (Glasgow Outcome Scale 1), 29.2% in the nimodipine group compared with 9.8% in controls. There was no difference in mortality rates in the grades IV–V nimodipine and placebo treated patients, but 28% of the grade III nimodipine patients died, compared with 4.8% given placebo.

Subsequently, the British aneurysm nimodipine trial (BRANT), in which 554 patients with SAH were analyzed, found that treatment with oral nimodipine was associated with a significantly lower rate of cerebral infarction: 22% in the nimodipine group compared with 33% in the placebo group. There was also an overall 40% reduction in poor outcome at the 3-month follow-up in patients treated with nimodipine. Critics have pointed out that a ruptured aneurysm was not proven to be the cause of SAH in 34% of the patients. Although this observation is true, it would only serve to dilute the potential beneficial effect of nimodipine since the incidence of infarction from vasospasm is generally lower in non-aneurysmal SAH.

Neither the BRANT study nor the other controlled trials with nimodipine found any differences in the incidence or severity of angiographic vasospasm. However, a beneficial effect from vasodilation of small arteries with improvement in collateral blood flow could not be excluded. Intravenous nimodipine-induced vasodilation of small pial arteries has been observed intraoperatively in a double-blind, placebo-controlled study of 16 patients undergoing extracranial-intracranial bypass surgery. Also, in 40 patients undergoing clipping of ruptured intracranial aneurysms who received intracisternal nimodipine, greater vasodilation was produced in the smaller cerebral arteries compared with the larger basal cerebral arteries, including arteries with segmental vasospasm. Alternatively, or in addition, a neuronal protective effect, as discussed above, may explain the apparent benefit.

There have been several uncontrolled series investigating the use of intravenous nimodipine for treatment of cerebral vasospasm associated with aneurysmal SAH. In several of the series, intraoperative intracisternal nimodipine was used along with early aneurysm surgery whenever possible. Gilsbach included induced hypertension by use of dobutamine, and Seiler used intentional hypervolemia for treatment of vasospasm. These studies suggested that there may be a potential role for intravenous nimodipine for treatment of vasospasm, but the conclusions were limited because of the absence of controls. Subsequently, in a randomized, double-blind, placebo-controlled study of intravenous nimodipine, Jan reported that in 127 SAH patients treated with nimodipine after onset of symptomatic vasospasm or documented angiographic vasospasm, there was a statistically significant 37% risk reduction of poor outcome and 83% risk reduction of mortality due to vasospasm (Table 1). Unfortunately, when the 61 SAH patients excluded from the study because of protocol violations were considered in the analysis, the reduction in poor outcome and mortality due to vasospasm became only trends and were no longer statistically significant. In a double-blind, placebo-controlled trial with intravenous nimodipine in 213 good grade aneurysmal SAH patients, Ohman found no difference in overall outcome between the nimodipine and placebo groups although there was an
<table>
<thead>
<tr>
<th>Study</th>
<th>Nimodipine treatment</th>
<th>Total patients</th>
<th>Exclusions</th>
<th>Placebo</th>
<th>Nimodipine</th>
<th>Admit neurologic grade</th>
<th>Interval to treatment after SAH</th>
<th>Follow-up period</th>
<th>Assessment scale</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen</td>
<td>P.O. 0.35 mg/kg q 4 hr×21 days</td>
<td>125</td>
<td>9</td>
<td>60</td>
<td>56</td>
<td>I–II</td>
<td>≤96 hr</td>
<td>21 days</td>
<td>5-step</td>
<td>(GOS 1–2)</td>
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<tr>
<td>Philippon</td>
<td>P.O. 60 mg q 4 hr×21 days</td>
<td>170</td>
<td>90</td>
<td>39</td>
<td>31</td>
<td>I–III</td>
<td>≤72 hr</td>
<td>21 days</td>
<td>GOS</td>
<td>(GOS 1–2)</td>
</tr>
<tr>
<td>Neil-Dwyer</td>
<td>P.O. 60 mg q 4 hr×21 days</td>
<td>75</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>I–V</td>
<td>≤96 hr</td>
<td>21 days</td>
<td>GOS</td>
<td>(GOS 1–2)</td>
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<tr>
<td>Petruk</td>
<td>P.O. 90 mg q 4 hr×21 days</td>
<td>188</td>
<td>34</td>
<td>82</td>
<td>72</td>
<td>III–V</td>
<td>≤96 hr</td>
<td>21 days</td>
<td>GOS</td>
<td>(GOS 1–2)</td>
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<tr>
<td>BRANT</td>
<td>P.O. 60 mg q 4 hr×21 days</td>
<td>1,115</td>
<td>561</td>
<td>276</td>
<td>278</td>
<td>I–IV</td>
<td>≤24 hr after diagnosis of vasospasm</td>
<td>21 days</td>
<td>GOS</td>
<td>(GOS 1–2)</td>
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<tr>
<td>Jan</td>
<td>I.V. 0.03 mg/kg/hr×7–14 days</td>
<td>127</td>
<td>61</td>
<td>54</td>
<td>73</td>
<td>I–III</td>
<td>≤10 days</td>
<td>3 mo</td>
<td>GOS</td>
<td>(GOS 1–2)</td>
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<tr>
<td>Ohman</td>
<td>I.V. 15–30 μg/kg/hr×7–10 days, then P.O. 360 mg/day×11–14 days</td>
<td>213</td>
<td>2</td>
<td>109</td>
<td>104</td>
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**Results**

<table>
<thead>
<tr>
<th>Favorable outcome</th>
<th>Poor outcome</th>
<th>Death</th>
<th>Relative risk reduction in poor outcome</th>
</tr>
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<tbody>
<tr>
<td>(GOS 1–2)</td>
<td>(GOS 1–2)</td>
<td>(GOS 1–2)</td>
<td>(GOS 1–2)</td>
</tr>
<tr>
<td>N19 (76%)</td>
<td>N28 (39%)</td>
<td>N23 (80%)</td>
<td>N49 (67%)*</td>
</tr>
<tr>
<td>P13 (52%)</td>
<td>P28 (34%)</td>
<td>P185 (67%)</td>
<td>P26 (48%)*</td>
</tr>
<tr>
<td>N1 (2%)*</td>
<td>N3 (10%)*</td>
<td>N1 (4%)</td>
<td>N7 (10%)*</td>
</tr>
<tr>
<td>P8 (13%)*</td>
<td>P13 (33%)*</td>
<td>P12 (48%)</td>
<td>N10 (10%)</td>
</tr>
<tr>
<td>N1 (2%)*</td>
<td>N3 (10%)*</td>
<td>N1 (4%)</td>
<td>N10 (10%)</td>
</tr>
<tr>
<td>P3 (5%)*</td>
<td>P7 (18%)*</td>
<td>P6 (24%)</td>
<td>P20 (37%)*</td>
</tr>
<tr>
<td>(86%)*†</td>
<td>(71%)*†</td>
<td>50%</td>
<td>37%†</td>
</tr>
</tbody>
</table>

BRANT, British Aneurysm Nimodipine Trial; GOS, Glasgow Outcome Scale; NR, not reported; N, nimodipine; P, placebo.

*Patients with vasospasm only.
†Statistically significant p < 0.05.
88% reduction in mortality rate due to vasospasm in the nimodipine group (Table 1). In a subgroup analysis of the timing of aneurysm surgery, there was an 87% decrease in mortality rate in 62 nimodipine treated patients undergoing early surgery compared with 65 controls also having surgery within 1 week of SAH.

There has been great interest in the use of nicardipine for treatment of vasospasm due to aneurysmal SAH in the United States because of its water solubility and potential for intravenous use in contrast to nimodipine, which requires an alcohol/ethylene glycol vehicle for intravenous use. In a dose-escalation study of nicardipine in 67 patients with aneurysmal SAH, Flamm reported a dose-related trend toward benefit with only 2 of 33 (6%) patients treated with a dose of 10 mg/hr developing symptomatic vasospasm compared with 9 of 34 (27%) patients treated at lower doses. Currently, 46 North American participants in the Cooperative Aneurysm Study have accumulated over 800 patients in a multicenter, prospective, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of intravenous nicardipine for treatment of vasospasm associated with aneurysmal SAH. Patients in all neurologic grades and intervals to admission up to 7 days are eligible for entry. This study should also yield valuable information about whether treatment with induced hypertension and/or intentional hypervolemia and hemodilution is compatible with the concurrent use of nicardipine. This is of importance since several uncontrolled studies have suggested that various regimens to induce hypertension, hypervolemia, and hemodilution may be beneficial in the treatment of symptomatic vasospasm.

Nonhemorrhagic Cerebral Infarction

Calcium antagonists are not yet approved for use in the treatment of nonhemorrhagic cerebral infarction, but several preliminary studies have suggested that they are a promising potential treatment of ischemic strokes. A small, single-blind, placebo-controlled pilot study by Gelmers in 1984 suggested that treatment with oral nimodipine was associated with decreased neurologic disability in 60 patients with nonhemorrhagic cerebral infarction. Subsequently, in 1988 Gelmers reported a prospective, double-blind, randomized, placebo-controlled trial of nimodipine in 186 patients with treatment starting within 24 hours of the onset of symptoms of acute ischemic cerebral infarction. Nimodipine treatment was associated with a 58% reduction in mortality in men and improved neurologic outcome in patients with moderate to severe deficits at the start of treatment. At least three multicenter randomized, controlled trials of nimodipine for acute cerebral infarction have recently been completed, and the results are anxiously awaited.

In a double-blind, randomized, pilot study of PY 108-068 involving 19 patients with acute cerebral infarction, patients receiving oral PY 108-068 had improved neurologic outcome compared with controls. A subsequent multicenter, prospective, double-blind, randomized, placebo-controlled clinical trial of PY 108-068 has been completed with data presently being analyzed.

An uncontrolled, dose-escalation safety study using intravenous followed by oral nicardipine in 58 patients treated within 12 hours of onset of symptoms of ischemic stroke has been completed. Doses up to 3–4 mg/hr were well tolerated. A randomized, controlled, clinical trial of nicardipine for acute cerebral infarction is in the planning stages.

Conclusions

The cerebroselective calcium antagonists are a promising new class of drugs that may have a major role in the treatment of stroke. Randomized clinical trials have suggested the efficacy of calcium antagonists for prevention or reduction of poor neurologic outcome due to vasospasm secondary to aneurysmal SAH. An interesting trend toward a multimodal therapeutic approach for the treatment of aneurysmal SAH is developing with early aneurysm surgery to prevent rebleeding, calcium antagonists to prevent cerebral infarction due to vasospasm and induced hypertension, intentional hypervolemia, and hemodilution to treat symptomatic vasospasm. However, further investigation is necessary to determine whether this approach is the best and if these therapies are compatible. Additional information is still required to support a therapeutic role of calcium antagonists to improve neurologic outcome in acute ischemic cerebral infarction.

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