Implications of nimodipine prophylaxis of cerebral vasospasm on anesthetic management during intracranial aneurysm clipping

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Nimodipine, a calcium entry blocking agent similar in structure to nifedipine but with selective cerebrovascular dilating effects, has potential use in the therapy and prevention of cerebral vasospasm after intracranial hemorrhage. The authors summarize the effects of calcium entry blockers, review the pharmacology of nimodipine, and discuss both the known and possible interactions of oral nimodipine with physical and pharmacological interventions that neuroanesthesiologists employ for patients with cerebral vasospasm during craniotomy for aneurysm clipping.

In a series of 26 patients undergoing aneurysm clipping, the authors found that intraoperative blood pressure tended to be reduced by nimodipine. Although the number of patients was limited by the fact that they were enrolled in a multi-center nimodipine aneurysm study and thus had to meet the criteria for that study, it is concluded that prophylaxis of cerebral vasospasm with nimodipine in patients with ruptured intracranial aneurysm results only in a favorable tendency toward lower systemic blood pressure during craniotomy.

KEY WORDS • anesthesia • aneurysm clipping • cerebral vasospasm • nimodipine • blood pressure • calcium entry blocker

Until recently, calcium entry blocking agents were primarily used in the perioperative period for management of myocardial ischemia and cardiac arrhythmias. The calcium entry blockers verapamil, nifedipine, and diltiazem have been studied clinically for several years in the United States, where they are used in the management of patients with angina pectoris, myocardial infarction, and paroxysmal supraventricular tachycardia, and for myocardial preservation during short-term disruption of coronary perfusion for aortocoronary bypass grafting. The current and proposed indications for the use of these agents are shown in Table 1.

Nimodipine, a structural derivative of nifedipine, exerts selective cerebrovascular dilating effects. The demonstration that nimodipine prevents cerebral vasospasm after subarachnoid hemorrhage mandates an understanding of calcium entry blockers by both neurosurgeons and neuroanesthesiologists. The purpose of this review is to summarize the clinically important features of calcium entry blockers, to review the pharmacology of nimodipine, and to discuss the possible interactions of nimodipine with anesthetic management of patients undergoing craniotomy for aneurysm clipping.

General Pharmacology of Calcium Entry Blockers

Myocardium, vascular smooth muscle, the sinoatrial node, and the atrioventricular node are all tissues that have little intracellular calcium and must depend on influx of calcium ions (Ca++) for depolarization. Approximately 5% to 10% of the amount of Ca++ necessary for maximal contraction of vascular smooth muscle and cardiac muscle enters during Phase 2 depolarization of the cell membrane following rapid sodium ion (Phase 0) and chloride ion (Phase 1) influx. These Ca++ channels are termed “slow channels” since Ca++ influx is slower to occur and occupies a greater portion of the duration of the action potential than influx of other ions.

In cardiac sarcomeres, Ca++ entering with membrane depolarization induces a large intracellular release of
the Ca++ stored in the cisterns of the sarcoplasmic reticulum. 3, 25, 26 This surge of Ca++ interacts with the myocardial contraction-regulatory protein, troponin, thereby allowing actin and myosin to activate adenosine triphosphatase (ATPase) and thus provide energy for contraction. 12 By way of the smooth muscle contraction-regulatory protein, calmodulin, Ca++ induces phosphorylation in vascular smooth muscle of myosin, which can then interact with actin and cause contraction by way of ATPase activation. 1, 11, 12, 18, 45

Calcium entry blockers decrease the transmembrane influx of Ca++ during Phase 2 depolarization, thereby restricting the amount of intracellular Ca++ available for activation. 3 This sequence is the primary mode of action of nifedipine. In addition, verapamil and diltiazem alter repolarization of the Ca++ gate, and possibly have other intracellular effects as well. 3 As a consequence, all these drugs specifically and exclusively affect those tissues that rely on the entry of extracellular Ca++ for depolarization, and they thus directly depress myocardial contractility, decrease systemic vascular resistance, and decrease sinoatrial and atrioventricular nodal function. 15, 21, 41

All calcium entry blockers directly decrease myocardial contractility, an effect that may be reversed by the administration of CaCl2. 15 However, when these agents are given to patients with normal ventricular function, cardiac output may actually increase because the negative inotropic effects are counterbalanced by vasodilation and reflex sympathetic stimulation of the myocardium. In patients with impaired ventricular function, nifedipine significantly reduces pulmonary artery wedge pressure, and improves left heart output by reducing afterload. 3, 20, 34

The most prominent hemodynamic action of most calcium entry blockers is to lower systemic blood pressure by reducing systemic vascular resistance, 28, 34, 36, 38, 46 since vascular beds are dilated to some extent by all calcium entry blockers. Calcium antagonists have little effect on venous capacitance vessels, in contrast to nitrates, which cause marked venodilation. 36, 43

However, the reduction in blood pressure by calcium entry blockers may produce reflex adrenergic stimulation (Table 2). The net effects of these drugs, therefore, represent a balance between direct depressant effects on calcium entry-dependent functions and indirect reflex adrenergic effects (Table 3). 3 Inhibition of direct calcium-dependent membrane excitation accounts for the depressant effect of calcium entry blockers on sinus node automaticity. Interference with the excitation-contraction coupling process accounts for the negative inotropic activity. The effects of calcium entry blockers on vascular smooth muscle may result from either inhibition of excitation-contraction coupling or suppression of calcium-dependent smooth-muscle activity. 3

Nifedipine causes the greatest amount of peripheral vasodilation, thereby inducing more baroreceptor activity to mask negative inotropic or chronotropic effects. Indeed, studies have shown that nifedipine can be safely used in patients with poor myocardial contractility, reflected in ejection fractions of less than 30%. 24, 28, 41 In contrast, verapamil elicits less reflex stimulation and causes more apparent myocardial depression, particularly in patients with preexisting myocardial dysfunction. 10, 23, 24, 38 Diltiazem lacks apparent negative inotropic effects. 30 The peripheral hemodynamic effect of nimodipine appears similar to, but less than, that of nifedipine. 14

The pharmacological effects of the calcium entry blockers depend not only on direct and indirect effects but also on selectivity for different tissue slow channels. For example, nifedipine increases heart rate without

TABLE 1

<table>
<thead>
<tr>
<th>angina pectoris</th>
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<tr>
<td>vasospastic</td>
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<tr>
<td>classic</td>
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<tr>
<td>supraventricular tachyarrhythmias</td>
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<tr>
<td>hypertension</td>
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<td>pulmonary</td>
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<td>hypertrophic cardiomyopathy</td>
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<td>cerebral vasospasm after subarachnoid hemorrhage</td>
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<td>calcium-mediated cellular damage</td>
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<td>after infarction</td>
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<td>during cardiopulmonary bypass</td>
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<tr>
<td>brain</td>
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<td>anoxic/ischemic insult</td>
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TABLE 2

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<tr>
<th>Direct Effects</th>
<th>Indirect Effects</th>
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<tr>
<td>myocardial contractility</td>
<td>myocardial contractility</td>
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<tr>
<td>heart rate</td>
<td>heart rate</td>
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<tr>
<td>atrioventricular conduction</td>
<td>atrioventricular conduction</td>
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<tr>
<td>vascular tone</td>
<td>vascular tone</td>
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* I = decreased; ↑ = increased. |
† Reflex sympathetic response to decreased blood pressure.

TABLE 3

<table>
<thead>
<tr>
<th>Effect</th>
<th>Verapamil</th>
<th>Nifedipine</th>
<th>Diltiazem</th>
<th>Nimodipine</th>
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<tr>
<td>inotropy</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>chronotropy</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
<td>↑↑</td>
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<tr>
<td>dromotropy</td>
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<td>±</td>
<td>↓</td>
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<td>systemic vascular tone</td>
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<td>±</td>
<td>↑↑</td>
<td>±</td>
<td>↑</td>
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<tr>
<td>coronary vasodilation</td>
<td>+</td>
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<td>+</td>
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* Summary of data from published studies. 3, 13, 19, 41
† = variable; ↑ = increased; ↓ = decreased; ± = equivocal; + = present.
altering the velocity of atrioventricular nodal conduction. Indeed, the tachycardia after nifedipine administration may be substantial enough to precipitate myocardial ischemia in patients with stable angina. The vascular smooth muscle is much more susceptible than the atrioventricular node or the myocardium to nifedipine, the vasodilation and reduced blood pressure caused by nifedipine evoke a sympathetic (adrenergic) reflex that counteracts nifedipine's negative chronotropic and dromotropic actions. In summary, the primary hemodynamic effects of calcium channel blockers include variable decreases in mean arterial pressure and systemic vascular resistance, accompanied by decreases in heart rate, cardiac output, and contractility that are modified by indirect sympathetic reflex effects. The cardiovascular effects of calcium entry blockers are summarized in Table 3.

Cerebral and Systemic Effects of Nimodipine

Nimodipine differs from commercially available calcium entry blockers in that it dilates the cerebral vasculature to a greater extent than the peripheral vasculature. Harper, et al., reported that nimodipine given as a constant infusion of 2 µg/kg/min slightly dilated the cerebral vessels of normal baboons without affecting cerebral metabolism. When the blood-brain barrier was osmotically disrupted, nimodipine proved to be a potent cerebral vasodilator, again without metabolic effects. They speculated that nimodipine might have important beneficial effects in ischemic brain regions where blood-brain barrier dysfunction can be anticipated.

Nimodipine is an effective dilator of the cerebral vasculature even when profound vasoconstriction is present. Steen, et al., produced 10 minutes of complete ischemia in dogs by temporarily ligating the aorta and vena cava, and studied the effects of preischemia administration of nimodipine on cardiovascular variables, cerebral blood flow (CBF), and recovery from the ischemic neurological injury. Immediately before aorticocaval occlusion, the dogs were given nimodipine, 10 µg/kg intravenously, followed by an infusion of 1 µg/kg/min for 2 hours. Posts ischemic CBF and metabolism were measured for 120 minutes in six dogs. Neurological recovery was evaluated 48 hours posts ischemia in five dogs. The results were compared with those previously determined in seven control dogs. Nimodipine nearly doubled CBF in the delayed posts ischemic hypoperfusion period, but had no significant effect on cerebral metabolism. Nimodipine also improved neurological recovery. Four of five treated dogs were normal neurologically and one was moderately damaged, whereas six of seven control dogs were either severely damaged or dead. This suggests that the delayed hypoperfusion state occurring after complete cerebral ischemia probably does contribute to the ultimate extent of neurological damage, and that nimodipine may be a useful therapeutic agent in limiting posts ischemic cerebral hypoperfusion. Since the systemic hemodynamic effects of nimodipine were minimal, the drug may ultimately prove to be useful after cardiopulmonary resuscitation. However, a follow-up trial of nimodipine administered to dogs 2 minutes after restoration of flow showed a decreased therapeutic effect.

Little information is available regarding the hemodynamic effects of nimodipine in man. Allen, et al., identified no adverse hemodynamic responses in 56 patients who completed a 21-day course of oral nimodipine therapy. Guggiari, et al., studied the effects on systemic hemodynamics and intracranial pressure (ICP) of nimodipine administered to 10 head-injured patients in an intensive care unit. Their patients had normal ICP at the time of the study, at least 2 weeks postinjury. The PaCO2 was maintained by mechanical ventilation at 30 mm Hg during the study. After 30 minutes of steady-state measurements, a 1-µg/kg/min loading dose of nimodipine was injected over 10 minutes, followed by a continuous infusion of 0.5 µg/kg/min over 4 hours. The hemodynamic and ICP changes produced by the loading dose in that study are shown in Table 3; these changes persisted during 4 hours of continuous drug infusion.

The hemodynamic data presented by Guggiari, et al., suggest that intravenous nimodipine, to a somewhat lesser extent than nifedipine, acts as a systemic vasodilator in man. Systemic arterial resistance and mean arterial pressure (MAP) are decreased, producing a reflex tachycardia. The increase in ICP is more striking than the slight change in systemic hemodynamics. These data imply a direct effect of nimodipine on human cerebral blood volume, an effect that is supported by direct observation of dilation of pial vessels during craniotomy in patients treated with nimodipine.

Nimodipine Pretreatment in Aneurysm Clipping

Patients who require general endotracheal anesthesia for clipping of an intracranial aneurysm present two sets of conflicting goals for the anesthesiologist. The first goal is to avoid promotion of cerebral vasospasm and the second is to maintain cerebral perfusion pressure (MAP — ICP) within a range that maintains adequate CBF without precipitating aneurysmal rupture. The first goal is necessitated by the fact that cerebral vasospasm plays a significant part in preoperative and
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postoperative morbidity following subarachnoid hemorrhage.7 The second goal is a function of the necessity for higher perfusion pressure in areas of vasospasm and of the extent to which obstructive hydrocephalus, intracranial hematomas, or cerebral edema have decreased intracranial compliance.6 For example, potent inhalational agents decrease cerebral metabolism and/or are cerebral vasodilators; as a consequence, they have theoretical advantages in patients at risk for vasospasm7,31,44. However, cerebral ischemia could result from the combination of a decreased MAP and increased ICP due to cerebral vasodilation and increased cerebral blood volume.6 Similarly, although mild hypertension may encourage blood flow through spastic cerebral vessels,12,35 excessive hypertension may precipitate rupture of an aneurysm.15 Despite the often tenuous balance between the risk of aneurysm rupture and the risk of cerebral ischemia, pharmacological hypotension, usually achieved with sodium nitroprusside, is often deliberately established to lessen the likelihood of rupture of an aneurysm during the surgery.13

Other physiological variables also require difficult decisions. An increase in PaCO2 may increase cerebral blood volume and ICP in a brain already compromised compliance. A decrease in PaCO2 may decrease brain bulk and permit easier surgical dissection, but may also increase transmural pressure in the aneurysm.6 The net effects of adding the influence of a cerebral vasoconstrictor are difficult to predict. It is possible that reduction in PaCO2 will set up “inverse steal,” thereby redirecting flow to ischemic areas.27 The opposite effect might occur with hypercarbia. The effects of changes in PaCO2 on hemorrhage-induced vasospasm have not been established.

Anesthetic induction agents pose similar problems. Sodium thiopental is an excellent anesthetic agent for neurosurgical procedures because of its ability to decrease cerebral metabolic consumption of oxygen and to produce cerebral vasoconstriction.27,33 These effects are particularly valuable in patients with increased ICP, such as those with intracranial hematomas or those who may be subjected to the short-term risk of cerebral ischemia. No tendency for the cerebral vasoconstrictor effects of sodium thiopental to potentiate cerebral vasospasm in the presence of subarachnoid hemorrhage has been demonstrated.

Nimodipine could influence the anesthetic management of patients undergoing aneurysm surgery in several ways. First, because of its mild systemic vasodilator effects, nimodipine could decrease the hypertensive response to intubation and to surgery. Similarly, nimodipine might decrease requirements for vasodilator drugs. Because intraoperative blood pressure should tend to be lower if nimodipine has been used preoperatively, apparent anesthetic requirements (usually assessed by hemodynamic changes) might be decreased. Finally, the cerebral vasodilating effects of nimodipine might provide better CBF during deliberate intracranial hypertension and, should cerebral ischemia occur, might provide cerebral protective effects such as those noted by Steen, et al.40 The potential effects of nimodipine pretreatment can be summarized as follows: 1) increased fluid and blood requirements; 2) decreased hypertensive response to noxious stimuli; 3) decreased amount of anesthetic agent(s) required; 4) decreased amount of hypotensive agent(s) required; and 5) decreased ischemic neurological damage sustained.

Summary of Cases

We studied the effects of nimodipine in a clinical series of 26 patients undergoing clipping of intracranial aneurysms. These patients were enrolled in a multicenter double-blind randomized placebo-controlled trial of oral nimodipine for 21 days after aneurysm rupture. Of the 26 patients, 14 received nimodipine and 12 were given a placebo: 0.7-mg/kg loading dose followed by 0.35 mg/kg every 4 hours.2 We retrospectively compared the following variables: 1) total intraoperative fluid requirements; 2) peak hypertensive responses to intubation, incision, and a low blood pressure level during a period of minor stimulation before incision; 3) maintenance requirements for potent inhalational anesthetics; and 4) vasodilator requirements. Vasodilator requirements could be compared only qualitatively due to the different surgical requirements for depth and duration of deliberate hypotension in each patient. Anesthetic maintenance requirements were compared using the following formula:

\[
\text{MAC equivalents} = \frac{C_{90-90}}{\text{MAC}} + \frac{C_{90-150}}{\text{MAC}} + \frac{C_{150-210}}{\text{MAC}} + 3,
\]

where MAC (maximum allowable concentration) = the average concentration of potent inhalational agents required to prevent movement in response to skin incision; C = average concentration of agent; and the subscript = the number of minutes after induction. Data were analyzed using Student’s t-test to compare fluid requirements and anesthetic requirements and multivariate analysis of variance of repeated measures to compare intraoperative hemodynamic responses (p < 0.05 was considered significant).

The nimodipine group required an average of 2330 ml of fluid during aneurysm clipping, while the placebo group required 2935 ml of fluid during clipping. Those differences were not significant.

Maintenance anesthetic requirements in the two groups were nearly identical. The nimodipine group required 0.78 ± 0.07 MAC equivalents, whereas the placebo group required 0.77 ± 0.01 MAC equivalents. There were also no apparent differences in the dose of sodium nitroprusside required to decrease blood pressure.

The intraoperative hemodynamics are summarized in Fig. 1. Baseline systolic blood pressure was nearly identical in the two groups. The peak blood pressure after intubation and the peak blood pressure after incision showed a strong trend toward higher levels in the
placebo group (p = 0.07 and 0.06, respectively). The minimal blood pressure that was maintained during the period of mild stimulation was significantly lower in the nimodipine group (p = 0.048). Upon the patients' awakening, and throughout their remaining stay in the recovery room, the intensive care unit, and the hospital, there were no significant differences in systolic blood pressure between groups. Diastolic blood pressure was similar throughout the intraoperative period. There were no differences in postoperative neurological status between patients in the placebo group and those in the nimodipine group. In each group, one patient died and one had a moderate deficit. The other 12 of the 14 nimodipine-treated patients and the other 10 of the 12 placebo patients had an excellent outcome.

In this series, nimodipine had no apparent deleterious effects on the perioperative course. It tended to limit the hypertensive response to stimulation, a characteristic that is desirable in patients at risk for rebleeding from intracranial aneurysms. The significantly lower minimal blood pressure seen before incision can be managed easily by limiting the dose of potent inhalational agent prior to stimulation. Had the series been one had a moderate deficit. The other 12 of the 14

![Graph showing Systolic Blood Pressure over time](image)

**FIG. 1. Effect of nimodipine (14 patients) or placebo (12 patients) on perioperative systolic blood pressure in patients undergoing intracranial aneurysm clipping.**

Conclusions

Calcium entry blockers exert a wide variety of useful pharmacological actions, among which the effect of greatest interest to neurosurgeons is the ability to provide prophylaxis against cerebral vasospasm. Nimodipine is at present the most promising of the calcium entry blockers for anti-vasospasm prophylaxis because of the high ratio of cerebral vasodilatory to systemic vasodilatory effect associated with it. The interaction of nimodipine with anesthetic management appears to be of little clinical consequence. The limitation of hypertension in response to intubation and incision that was effected by nimodipine is desirable, since hypertension may precipitate aneurysm rupture.

References

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