Early Treatment of Ischemic Stroke
With a Calcium Antagonist

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We performed a feasibility and safety study (phase II) of nicardipine, a calcium antagonist, in 57 patients. The objectives of the study were to begin therapy as early as possible (≤12 hours) after the onset of ischemic stroke and to administer as high a dose as possible. All patients received an intravenous infusion of nicardipine for 72 hours, starting with a dose of 3 mg/hr and increasing to a maximum dose of 7 mg/hr. Upward titration of the dose was limited by a 10% decrease in blood pressure or a 20 beats/min increase in pulse. Intravenous therapy was followed by 30 days of oral therapy. The mean ± SD interval from onset of stroke to commencement of therapy was 9.1 ± 5.4 hours. Adverse reactions consisted primarily of hypotension requiring discontinuation of therapy in four patients. Score on a graded neurologic examination increased from 41/100 at baseline to 64/100 at 3 months for the 41 patients completing follow-up. There was no correlation between the dose of nicardipine administered and outcome, but the 11 patients starting therapy ≤6 hours after onset did better than those starting therapy 6–12 hours after onset. Further study of very early therapy with nicardipine is justified. (Stroke 1991;22:437–441)

The demonstration of threatened but potentially viable tissue in both animal stroke models and stroke patients has stimulated interest in the therapy of acute cerebral ischemia. One strategy for preserving function in these brain regions is to increase cerebral blood flow (CBF). Another strategy is to block the damaging and possibly irreversible disruption of cellular homeostasis that results from the failure of energy-dependent membrane pumps.

Calcium antagonists are a group of drugs that may result in amelioration of ischemia by either or both mechanisms described above. One effect of these drugs' action is relaxation of vascular smooth muscle, which results in increased CBF. In addition, experimental studies suggest that calcium blockers prevent the intraneuronal accumulation of calcium during reperfusion after cerebral ischemia. The results of pharmacologic trials with these drugs in animal stroke models have been variable, with the best results found when the drug therapy was started before or immediately after ischemia.

A recently completed clinical trial of three different oral doses of the calcium antagonist nimodipine in 1,064 patients with acute cerebral infarction was negative when therapy was begun up to 48 hours after the onset of symptoms. However, subgroup analysis suggested that treatment with moderate doses (up to 120 mg/day) might be effective when started within 12 hours, and a study in the Netherlands was positive when treatment was started within 24 hours. The goals of the present open-labeled, nonrandomized study were to determine the safety and feasibility of treatment with nicardipine, a dihydropyridine calcium antagonist, administered intravenously to patients with moderately severe acute cerebral ischemia when treatment was initiated 12 hours after onset. This agent was chosen because of its water solubility and ease of intravenous administration.

Our specific objectives were 1) to assess the risks and side effects, in particular, the effect of nicardipine on blood pressure; 2) to determine the maximal tolerated dose and to correlate this dose with simultaneous blood levels; and 3) to determine the effect of nicardipine on patient morbidity (as measured by a standard grading scale), mortality, and infarct size (as measured on computed tomograms [CT scans]).

Subjects and Methods

We included all patients admitted to Hermann Hospital or St. Luke's Hospital, the principal teach-
ing hospitals affiliated with the University of Texas Medical School at Houston, or to the Barrow Neurological Institute in Phoenix, with the sudden onset of cerebral hemispheric symptoms consistent with cerebral infarction. Patients with presumed thrombotic/thromboembolic occlusions of large arteries, cardiogenic emboli, small-vessel disease, or ischemia of uncertain origin were eligible. Patients with symptoms referable to the vertebrobasilar territory were not included for reasons outlined by Sterman et al.15 Treatment was started ≤12 hours after the onset of ischemic symptoms.

On admission to the emergency room, the patient had a baseline graded neurologic examination performed. The stroke scale used (normal=100 points) was derived from a graded neurologic examination previously tested for interobserver variability and validity in patients with hemispheric cerebral infarction.16 All patients underwent a baseline head CT scan, chest roentgenogram, electrocardiogram, and screening laboratory tests (SMA-20, complete blood count, platelet count, prothrombin time, and partial thromboplastin time). An arterial line for blood pressure monitoring was placed as medically indicated.

Patients were excluded if they had a baseline graded neurologic examination score of >80 (i.e., mild deficit), if they were unarousable to voice, or if they had cerebral hemorrhage on the baseline CT scan. Patients were also excluded if they had a preexisting neurologic deficit that would interfere with the investigators' ability to determine the outcome of the acute cerebral infarction, if they had conorbid medical or psychiatric conditions that might limit their survival or follow-up for the next 3 months, or if they had an unstable cardiovascular condition, were already being treated with calcium antagonists, had a sensitivity to calcium antagonists, or were pregnant or nursing.

After the baseline measurement of mean arterial blood pressure (MABP), intravenous nicardipine mixed in half-normal saline was administered by a continuous infusion calculated to deliver 3 mg/hr. The rate was increased by 1 mg/hr every 15 minutes during upward titration of the drug to a maximum of 7 mg/hr. This dosing algorithm was based on results of the phase I studies and animal experiments.11,12,17 If two consecutive measurements of MABP were 10% lower than baseline and/or if the pulse rate rose by 20 beats/min above baseline, the infusion rate was stabilized. If MABP fell by >10%, the infusion rate was reduced. These criteria were established to prevent diminished cardiac output or significant hypoperfusion.

Throughout the infusion, the patient remained at bed rest with the head elevated 30° to avoid postural fluctuations in blood pressure. To prevent deep-vein thrombosis, all bedridden patients were treated with subcutaneous heparin, antiembolic stockings, and bedside physical therapy. There were no clinical occurrences of deep-vein thrombosis or pulmonary embolism in our patients. Adequate hydration was maintained in all patients by supplemental intravenous fluids. In the last nine patients treated, to correct any hypovolemia that might contribute to hypotension, up to 500 ml plasmapheresis was given daily if MABP fell by >10%. After 72 hours of intravenous drug therapy, a plasma nicardipine level was obtained and the infusion rate was tapered by 1 mg/hr every 60 minutes and then discontinued. As soon as the intravenous infusion was discontinued, oral nicardipine (30 mg t.i.d.) was begun. In those patients unable to swallow, the drug was given by emptying the capsule contents and administering them through an endogastric tube. Other standard treatments, such as antiplatelet agents/anticoagulants, antibiotics (where indicated), and supplemental oxygen (where indicated), were allowed as well as continuation of pretreatment medications. In most cases, however, preadmission antihypertensive medications were discontinued. Early intervention by physical, speech, and occupational therapy was encouraged.

The graded neurologic examination was performed daily during the 72 hours of intravenous drug administration and at 1 and 4 weeks and 3 months after the onset of the stroke. Disability as indicated by the Barthel index was also evaluated 1 and 3 months after the stroke.

Infarct volume on the baseline CT scan and CT scans taken 1 and 3 months after the stroke was calculated by outlining the area of low density on axial images and multiplying by the interimage distance (either 5 or 10 mm). For each CT slice, the total brain parenchyma area was also measured and the total brain parenchyma volume calculated.

Results

During the 18 months from July 1986 to December 1987, 385 consecutively admitted patients were screened and 62 patients were entered into the study; of these, five were subsequently excluded because they did not meet entry criteria (four had brain stem strokes and one had multiple sclerosis). No patient who met entry criteria refused to participate. Patient age ranged from 25 to 89 (mean 64) years; 29 were men and 28 women. The mean±SEM interval from onset of symptoms to commencement of therapy was 9.1±5.4 hours.

For 30 patients for whom data is available, the stroke was attributed to cardiac emboli in 13 patients (43%), large-vessel atherothrombosis in 7 (23%), large-vessel atheroemboli in five (17%), and small-vessel occlusion in three (10%); the cause was undetermined in two patients (7%). The diagnosis was made by the participating neurologist at each center at the 3-month evaluation based on all available clinical data. No standardized criteria were used when establishing these diagnoses.

There were seven deaths (12%), occurring from 4 to 65 days after stroke onset. All were due to the stroke itself or to medical complications related to the stroke. None could be directly related to nicardipine.

Adverse reactions consisted of hypotension (>10% decline in MABP) necessitating discontinuation of the
drug in four patients; none experienced neurologic deterioration. One patient each developed atrial flutter, nausea and vomiting, and liver function test abnormalities that were possibly related to the drug; the dose of nicardipine was not altered in these patients. No treatment was required in these three patients since the symptoms resolved spontaneously.

Mean systolic blood pressure for all patients receiving nicardipine dropped from 149±27 mm Hg at baseline to 142±22 mm Hg at 24 hours and 138±20 mm Hg at 72 hours. There were no clinically significant changes in laboratory values (hematology, coagulation, and blood chemistries) between those obtained at baseline and those obtained at 72 hours and 1 month except in the patient with elevated liver function values.

The mean±SEM total intravenous dose of nicardipine for all 57 patients was 228.5 ±117.9 mg over 72 hours. Infusion dose was compared with plasma level after 72 hours of therapy in 14 patients. In all instances, the patient had been receiving the indicated dose for at least 4 hours, so the blood levels represent a steady state (Figure 1). An infusion dose of 2-4 mg/hr (0.02-0.06 mg/kg/hr) resulted in a blood level between 75 and 125 ng/ml. This dose is similar to those used in animal studies (0.05 mg/kg/hr subcutaneously), which resulted in blood levels of 6-20 ng/ml. Therefore, with the intravenous dose used in this study blood levels were at least six times those achieved in animal studies in which benefit was shown.10,12,17

In the nine patients treated with nicardipine and plasmanate, the total intravenous dose of nicardipine over the 72 hours was 221.2±120.8 mg compared with 232.1±118.3 mg in the 48 patients treated with nicardipine and standard fluid management. Therefore, concomitant volume replacement did not increase the amount of nicardipine that could be given.

Of the initial 57 patients, seven died, four discontinued therapy, and five were lost to follow-up. Of the 41 patients completing 3 months of follow-up, mean ± SD score on the graded neurologic examination improved from 40.5±20.5 at baseline to 64.4±26.8 at 3 months. The mean percentage improvement in the 3-month score compared with baseline was 88% (Figure 2).

At the 3-month evaluation, seven (17%) of the patients had recovered completely, 24 (59%) had partially improved, 10 (24%) had stabilized, and none had become worse. Patient disability classification was no limitation in 16 (39%), mild limitation in 10 (24%), moderate limitation in 10 (24%), and severe limitation in five (12%). Overall, 33 (80%) of the patients were at home, and the mean Barthel index for the 41 patients was 70.

The 11 patients who started therapy ≤6 hours after stroke onset and completed 3 months of follow-up were compared with the 29 in whom therapy was delayed 6-12 hours. In one other patient, the exact time that therapy was begun could not be determined. The percentage improvement in score on the graded neurologic examination from baseline to 3 months was greater (133%) in those receiving the drug within 6 hours than in those receiving the drug later (71%, p=0.01, Student's t test). There was no dose–response relation found when either the total intravenous dose or the total intravenous plus oral dose was correlated with absolute or percentage change in score on the graded neurologic examination from baseline to 3 months.

For the 38 patients with CT infarct volume measurements, at the 3-month follow-up there was a significant negative correlation between infarct volume on CT and score on the graded neurologic examination (Figure 3, p<0.0001).

Discussion

This trial demonstrates that nicardipine may be given safely in doses that result in plasma levels greater than those showing increased CBF, some limitation of neuronal Ca entry, and functional improvement in an animal stroke model.10,12,17 However, unlike patients with subarachnoid hemorrhage, in whom doses as high as 15 mg/hr could be given, our patients demonstrated marked sensitivity to the hypotensive properties of nicardipine, which therefore limited the amount of drug that could be given.
There is concern that decreasing MABP may worsen infarction. However, none of our patients worsened neurologically, indicating that doses of 3–4 mg/hr and up to 10% decrease in MABP were tolerated.

The hypotension we observed indicates that the doses of nicardipine that we gave were sufficient to dilate blood vessels and possibly increase CBF. Although the brain concentration of nicardipine reflects the serum concentration, it is less certain that the doses given in this study were sufficient to block neuronal Ca	extsuperscript{2+} entry.

It was not the intent of this study to prove or disprove the efficacy of nicardipine. However, the outcome of patients in this study is encouraging. No patient worsened and 80% improved, with a mean increase of 88% from the baseline neurologic score to the 3-month follow-up score. One of the most important observations in this study was the difference between patients treated early (≤6 hours) and those treated later (6–12 hours). These results are consistent with results in animal studies and other human trials indicating that very early therapy is undoubtedly necessary to test properly the efficacy of calcium antagonists.

The infarct volume on CT has been shown to be an objective parameter for the assessment of outcome in stroke therapy trials. The results of this study support the use of CT for this purpose and corroborate the findings of a prior study using similar methodology.

There was no correlation between outcome at 3 months and the dose of nicardipine received, which was disappointing since a positive dose–response relation would give direct support for a beneficial biologic effect of the drug. However, it is possible that adverse cardiovascular effects of high-dose therapy (i.e., hypotension and reduced cardiac output) negated any beneficial effect. Therefore, there appears to be no advantage to risking hypotension by increasing the intravenous dose of nicardipine above 3–4 mg/hr.

The treatment of acute ischemic stroke with moderate intravenous doses of a calcium antagonist given early is possible, safe, and may be effective. However, despite optimal medical management, hypotension significantly limits the dose that can be given. Further trials of calcium antagonist therapy are needed, but it is clear that very early treatment and careful attention to avoiding adverse cardiovascular effects caused by high doses must be considered in the design of such studies.

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**References**


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