Clinical Trial of Nimodipine in Acute Ischemic Stroke

The American Nimodipine Study Group

Background and Purpose: A randomized, double-blind, multicenter clinical trial of placebo versus nimodipine was conducted to test the hypothesis that nimodipine would reduce the frequency of death and of worsening by 30% compared with placebo.

Methods: Nimodipine was used in doses of 60 mg, 120 mg, and 240 mg daily in 1,064 patients treated for 21 days. Treatment was begun within 48 hours of stroke due to infarction as inferred by initial computed tomographic scan findings. The Toronto and motor scales were analyzed by analysis of covariance, using covariance-adjusted means, the last-value-carried-forward, to compare the baseline value with the 3 assessment days (days 4, 10, and 21).

Results: No difference in mortality or neurological outcome was found with any of the rating scales for the overall cohort. Planned but post hoc subgroup analysis showed a reduction in worsening frequency of 30% compared with placebo and significantly better outcome scores with 120 mg nimodipine daily started within 18 hours of stroke as measured by the Toronto scale (p<0.005) and when the pretreatment computed tomographic scan was negative (p<0.003).

Conclusions: Nimodipine had no overall effect when treatment was begun within 48 hours. Confirmation of the benefits suggested by post hoc analyses for the subgroup treated with 120 mg nimodipine within 18 hours, and who had negative computed tomographic scans, would require a separate trial. (Stroke 1992;23:3-8)

Calcium antagonists offer the hope of reducing the severity of acute ischemic stroke. Nimodipine has adequate brain penetration, dilates intracranial vessels, and improves regional cerebral blood flow in the margins around cortical infarcts. Side effects, mostly minor, occur infrequently.

Early clinical trials in acute ischemic stroke used an oral dose of 120 mg per day (30 mg q.i.d. produces a blood level similar to the dose of 0.35 mg/kg every 6 hours used in subarachnoid hemorrhage trials) and evaluated patients by the Mathew scale. Gelmers et al treated 186 patients with 120 mg nimodipine within 24 hours and found fewer deaths compared with placebo at 28 days by Kaplan-Meier calculations (p<0.045) but found no significant overall difference in clinical outcome. Martinez-Vila et al randomized 123 patients after 24 hours and found no differences in mortality or morbidity. The Trust study, which entered 1,215 patients within 48 hours of stroke and used the N score, not the Mathew scale, showed a difference (p<0.05) favoring nimodipine at day 21 but not at follow-up week 24. Sherman et al undertook a small preliminary study with inconclusive results. The present study was organized to determine the safety and efficacy of nimodipine at daily doses of 60, 120, and 240 mg compared with placebo.

Subjects and Methods

Patients were eligible for the trial if they had an acute ischemic stroke within the preceding 48 hours, weakness against resistance in at least one limb, age 21–89 years inclusive, initial computed tomographic (CT) scan free of any evidence of brain hemorrhage or hemorrhagic infarction, and a reliable time of onset fixed by history or direct observation. The exclusion criteria were coma, intracranial hemorrhage, tumor, infection, trauma, serious organic brain disease other than ischemic cerebral infarction as defined by entry CT scan, need for mechanical ventilation, current use of calcium antagonist therapy, pregnancy, hypotension (systolic blood pressure <100 mm Hg), bradycardia (rate <50), second- or third-degree heart block if the patient did not have a pacemaker, clinically evident severe hepatic or renal dysfunction, and congestive heart failure or pneumonia diagnosed clinically or by chest x-ray.

Patients were randomized into four groups: a placebo group or a 60-mg, 120-mg, or 240-mg nimodipine (daily) group. A permuted block design was planned for 24 patients to be entered from each center. Study centers were provided numbered boxes...
Treatment was continued for 21 days, even if the group received four tablets of 20-mg nimodipine. nimodipine and two placebo; and the 240-mg nimodipine group received four tablets of 20-mg nimodipine. Treatment was continued for 21 days, even if the patient was discharged from the hospital. For patients diagnosed as having cardiogenic embolism, heparin was given for 3–5 days from admission and then replaced by warfarin therapy. Telephone follow-up at 3 and 6 months determined vital status.

Patients were seen daily for a formal but brief neurological examination during the in-hospital phase. Detailed examinations were performed at onset and on days 4, 10, and 21 using five separate neurological scales: the general neurological assessment from the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank; the motor strength scale from the Stroke Data Bank; and the Toronto and Mathew scales, used in their unmodified form. The Barthel Index was performed at day 21.

Repeat CT scan was undertaken between days 3 and 5 to seek confirmation of the diagnosis of ischemic stroke, evidence of hemorrhagic change, mass effect, or change in lesion site and size. Postrandomization exclusion was planned for patients misdiagnosed on admission and subsequently discovered to have intracranial hemorrhage, brain tumor, or other causes of an acute focal deficit inconsistent with acute ischemic infarction; or for those with a medical condition that precluded participation.

Sample size estimations were derived from the 30% frequency of worsening in the Harvard Stroke Registry10 and the population study of the NINDS Stroke Data Bank project11 and were based on the hypothesis that nimodipine would reduce this frequency by 30%. For four groups, a total of 1,252 patients would be required for an overall of 0.05 and a of 0.2 (power of 80%).

All patients, study center personnel, and those responsible for analysis were blinded as to drug code. The analysis focused on survival and clinical deficit severity. Mortality was measured by the percentage of patients surviving the first 21 days of treatment, with 3- and 6-month posttreatment survival as secondary variables. The Toronto Scale and the motor strength scale from the NINDS Stroke Data Bank were used as the primary indexes of neurological function. A simple calculation was made for the frequency of worsening, using a change of at least 5% from the baseline value toward a lower value on the Toronto score on day 4, the first day when full clinical reassessment was made using the standard scales.

A separate analysis was made of the course of the clinical deficit severity. This analysis did not incorporate the correction scores used in prior nimodipine studies. We selected the analysis of covariance because this method allowed us to take account of patients' initial and all subsequent scores. The average of days 4, 10, and 21, when standard evaluations were performed, was the measure of response, with the baseline value as the covariate. To account for missing values, we used the method of the last-value-carried-forward. For patients with data on days 4, 10, and 21, the measurement was the average of all three days. For data through day 10, the value on day 10 was assumed to apply to day 21 so that the resulting average gave the day 10 value twice the weight of the day 4 value. If data was obtained on days 10 and 21 but not day 4, the average was that of days 10 and 21. If data existed only on day 4, or day 10, or day 21, the average was the same as that day's result. Because all patients randomized and reaching day 4 evaluation were analyzed, including those not discovered to have been ineligible before day 4, the analysis followed the intent-to-treat principle. The trial was organized in July 1986, but actual data collection did not begin until October 1986. At the end of recruitment in March 1989, a total of 13,437 patients with acute stroke had been screened at 53 institutions. Of these, 1,064 patients were randomized.

Consistent with other studies, the peak hour of stroke onset was around 7 AM. The mean±SD time to start of treatment was 28.43±12.72 hours. Only 26 patients were treated within 6 hours, 163 within 12 hours, and similar numbers at 6-hour intervals thereafter (Table 1).

The clinical characteristics of the patients enrolled in the trial were equally distributed across the four treatment groups and approximated those of other clinical trials of stroke (Table 1). The mean age was 66 years; 58% of the patients were men; 65% were white and 25% black. The mean pulse was 78 beats per minute, blood pressure 151/85 mm Hg, and weight 76 kg. Twenty-five percent of the strokes were considered embolic in origin. The initial Glasgow Scale status showed one patient in a vegetative state, 80% dependent on others, 19% independent on activities of daily living, and 0.5% said to be essentially normal. The mean±SD initial Toronto score for the entire cohort was 71.93±52.90.

Twelve of the centers were in the trial >24 months, another 26 >18 months. Twenty-three centers entered more than 25 patients each, and the remainder entered fewer.

One hundred sixty-two patients (15.2%) died during the course of the study, including the 6-month follow-up period; of these, 64 died during the first 21 days of the study, and 36 died before day 4. Deaths were distributed widely throughout the 21-day phase of the study (mean, 11.6 days). By day 4, seven patients in the placebo group had died; eight patients in the 60-mg, seven in the 120-mg, and 14 in the 240-mg nimodipine groups had died. Overall, 42 in
the placebo group and 41 in the 60-mg, 37 in the 120-mg, and 42 in the 240-mg nimodipine groups died. The cause of death was cardiac in 45 patients, cardiopulmonary in 37, stroke in 36, infectious in 23, and other in 21.

The mean±SD time to discontinuation was approximately the same across the treatment groups: 9±5.88 days in the placebo group and 7.9±5.54, 8.7±6.27, and 7.6±5.4 days in the 60-, 120-, and 240-mg nimodipine groups, respectively. Experiences deemed "adverse" and believed by the investigator or patient to be related to the use of the test drug caused premature discontinuation in 126 patients (11.9%), of whom 48 died within 6 months of the index stroke. There were thirty-two discontinuations (12%) in the placebo group and 23 (8.7%) in the 60-mg, 32 (11.9%) in the 120-mg, and 39 (14.6%) in the 240-mg nimodipine groups. Of the 178 types of adverse events studied, those occurring in >5% of the 126 patients with adverse events were fever, headache, hypotension, constipation, and urinary tract infection. Blood pressure decline occurred most often in the first 24 hours and reached its stable state by day 4. The mean±SD decline from onset to day 4 was 6.67 SD±13.1 mm Hg in the placebo group and 6.80±12.9, 7.38±15.3, and 7.15±13.2 mm Hg in the 60-, 120-, and 240-mg nimodipine groups, respectively. The treatment groups, compared with the baseline pretreatment measurement, suffered roughly the same degree of hypotension, including the small subgroup with declines of >15 mm Hg.

Thirty-one patients suffered recurrent stroke: seven were in the placebo group; in the nimodipine-treated groups, six were in the 60-mg, 13 in the 120-mg, and five in the 240-mg group.

Illnesses deemed unrelated to the index stroke affected 66 patients, 14 in the placebo group and 16 in the 60-mg, 11 in the 120-mg, and 25 in the 240-mg nimodipine groups. Patient lack of cooperation caused 24 patients to be discontinued, seven each in the placebo and 240-mg nimodipine groups and five each in the 60-mg and 120-mg nimodipine groups. Of the twenty-one others who withdrew for other reasons, two were in the placebo group and seven in the 60-mg, nine in the 120-mg, and three in the 240-mg nimodipine groups.

Forty-two of the 1,064 patients (3.9%) were discovered later to be invalid for analysis. All the reasons for invalidity were protocol violations: failure to diagnose ischemic stroke, time of stroke to medication >48 hours, insufficient evidence of weakness on admission, incorrect study medication after day 1, <4 days treatment with of study drug, treatment with another calcium antagonist or major tranquilizer or antiplatelet agent, or the use of intravenous heparin for >1 day without evidence of cardioembolic stroke. Fifteen of these patients were identified and discontinued from participation before day 4. Data from the 27 discovered to have been ineligible on day 4 or later were included in the intent-to-treat analysis.

No data on clinical scales for days 4, 10, or 21 were collected in 102 patients (9.6%). Of these, 27 were in the placebo group and 25 each in the 60-mg, 120-mg, and 240-mg nimodipine groups. Thirty-six of these 102 patients had died before the time of data collection on day 4.
The intent-to-treat analysis was undertaken on data available on the remaining 962 patients, for whom data were collected on at least one of days 4, 10, or 21. Complete follow-up data (measurements on each of days 4, 10, and 21) were available for 726 of these patients. For the last-value-carried-forward calculations, data were available for days 4 and 10 for 103 patients, only day 4 for 109, days 10 and 21 for 12, days 4 and 21 for eight, and day 10 or day 21 for two patients each. The patterns of missing data were roughly evenly distributed across the treatment groups.

The primary hypothesis for the trial was not confirmed. No significant differences in outcome were found for the frequency of death or worsening between any dose of drug against placebo for the 1,064 patients randomized within the 48-hour time period. Nor was any difference found by clinical outcome measures using the Toronto, motor, or Matthew scale or the Barthel Index. The covariance-adjusted mean±SE for the Toronto score was 59.43±2.10 for the placebo group and 58.74±SE 0.82, 57.94±0.62, and 63.62±SE 0.16 for the 60-, 120-, and 240-mg nimodipine groups, respectively.

In preplanned subgroup analyses, statistically significant drug effects, adjusted for multiple tests by the Bonferroni method, were demonstrated for the major variables thought to be important in the infarct process tested by the Toronto scale. These variables were time to treatment, drug dose, and the presence or absence of a CT-positive lesion confirming infarction before the start of the trial. Those treated with 120 mg nimodipine within 18 hours showed a significantly lower frequency of worsening (18.6% versus 29.2%) on day 4 (the first day the standard neurological scales were reassessed) compared with the placebo group. This was the only subset supporting the pretrial hypothesis that nimodipine would reduce the frequency of worsening by 30% compared with placebo. The 120-mg nimodipine group treated within 18 hours also showed statistically significantly better scores compared with placebo, on the average, over the course of the trial by intent-to-treat analysis (Table 2). In a further subgroup analysis, the 120-mg nimodipine group treated within 18 hours who had an initially negative CT scan also showed a statistically significant effect compared with those who were CT-positive (Table 3).

**Discussion**

Our study is comparable to others in many, but not all, features. We and others did not experience the lower rates of mortality reported by Gelmers et al.
even though our 24-hour cohort was slightly larger than those in the Gelmers study. The main differences between our trial design and designs of others were in the scales used, details on CT scanning, and time to treatment in those instances where enough cases existed in the early time period to assess an effect.

Nimodipine was well tolerated in our trial. Because the discontinuation rate was approximately the same for the placebo group as for any dose of nimodipine, we infer that discontinuation was from participation in a trial, not from effects of the drug.

Overall, no statistically significant differences were seen in mortality or in any of the indexes of morbidity between placebo and any dose of nimodipine. However, planned analyses explored pretrial hypotheses that early treatment and an initially negative CT scan should predict a better response to drug. Although the sizes of the subgroups were small, statistically significant positive effects of possible clinical significance were found for the 120-mg nimodipine group treated within 18 hours of stroke onset. A further subset analysis suggested a benefit when the initial CT scan was negative but not when an initial CT scan was positive for infarction. Both findings suggest a treatment effect might occur if the tissue at risk has time to treatment in those instances where enough discontinuations and deaths in the 240-mg group may have pulled down the mean scores for this group, thus preventing a dose-response demonstration. It is also possible that the findings for the 120-mg group treated within 18 hours could be a statistical anomaly despite the Bonferroni corrections and despite observations that the positive findings occurred with early treatment and CT-negative status and not with other, less-biologically-relevant variables.

If nimodipine has a role to play in the treatment of acute ischemic stroke, no trial, including the present study, has yet documented it with certainty. Lacking alternatives to therapy, a trial to reexplore the effects of early therapy, in a CT-negative cohort, with an oral dose of 120 mg nimodipine could clarify the meaning of the subgroup findings in our trial.

Appendix

Study Participants

- M Alter, Medical College of Pennsylvania, Philadelphia, Pa.; M Agius, University of Chicago Medical Center, Chicago, Ill.; HM Barlow, Riverside Methodist Hospital, Columbus, Ohio; B Baumel, Neuromedical Research Institute, Miami Beach, Fla.; J Biller, University of Iowa Hospitals and Clinics, Iowa City, Sw; SW Boyer, The Jackson Clinic, Madison, Wis.; WA Bradley, University of Vermont, Montpelier; LM Brasa, Yale-New Haven Hospital, New Haven, Conn.; R Brenan, Pennsylvania State University, Hershey; JA Byer, University of Missouri Hospital, Columbus, Ohio; CS Chester, Cleveland Metropolitan General Hospital, Cleveland, Ohio; SN Cohen, West Los Angeles Veterans Affairs Medical Center, Los Angeles; J Couch, Southern Illinois University, Springfield, Ill.; A Culebras, Virginia Medical Center, Syracuse, N.Y.; B Dobkin, Reed Neurological Research Center, Los Angeles, Calif.; MP Earnest, Denver General Hospital, Denver, Colo.; JH Feibl, Christ Hospital Medical Building, Cincinnati, Ohio; W Feinberg, University of Arizona Health Science Center, Tucson, Ariz.; M Gomez, St. Louis University, St. Louis, Mo.; PGorelick, Michael Reese Hospital, Chicago, Ill.; J Grotta, University of Texas Health Science Center, Houston; ER Hackett, Louisiana State Medical Center, New Orleans; EC Haley Jr., University of Virginia, Charlottesville; JA Halsey, University of Alabama Hospital, Birmingham; J Hamilton, University of South Alabama Medical Center, Mobile; L Hershay, Veterans Affairs Hospital, Buffalo, N.Y.; J Hollander, Rochester General Hospital, Rochester, N.Y.; S Horowitz, St. Vincent Hospital, Worcester, Mass.; CY Hsu, Medical University of South Carolina, Charleston; RL Hughes, Ochsner Clinic, New Orleans, La.; CS Kase, Boston University School of Medicine, Boston, Mass.; J Miller, North Indiana Neurological Institute, Merrillville; A Miller, Maimonides Medical Center, Brooklyn, N.Y.; P Karanjia, Marshfield Clinic, Marshfield, Wis.; R Kelley, University of Miami, Miami, Fla.; NS Low, Albany Medical College, Albany, N.Y.; MA Fisher, Worcester Memorial Hospital, Worcester, Mass.; JF Mohr, New York Neurological Institute, New York; PMunschauer, Erie County Medical Center, Buffalo, N.Y.; PT Nichols, Medical College of Georgia, Augusta; KL Nudelman, Irvine Medical Center, Orange, Calif.; RM Ramirez-Lasstap, St. Paul-Ramsey, St. Paul, Minn.; JT Robertson, University of Tennessee, Memphis; DM Rosenbaum, Montefiore Medical Center, Bronx, N.Y.; J Rothrock, University of California, San Diego; J Russell, Guthrie Clinic, Sayre, Pa.; V Saxena, Froedert Hospital, Milwaukee, Wis.; G Sheppard, Winchester Medical Center, Winchester, Va.; DSherman, University of Texas Health Science Center, San Antonio; BT Troost, Bowman Gray School of Medicine, Winston-Salem, N.C.; TM Walsh, Brockton Veterans Affairs Medical Center, Brockton, Mass.; C Wasterlain, Sepulveda Veterans Affairs Hospital, Sepulveda, Calif.; KMA Welch, Henry Ford Hospital, Detroit, Mich.; PWolfson, Chicago College of Osteopathic Medicine, Chicago, Ill.

Acknowledgments

This work was supported by Miles Inc., West Haven, Conn. Data analysis was supported in part by a gift from the Horace W. Goldsmith Foundation and the Remin Fund. This study was conducted by Bayer AG and Miles Inc. JF Mohr, MD, served as scientific adviser, principal investigator, and author of the manuscript. J.L. Muschett and R.V. Riccio of G.H. Besselaar Associates, Princeton, N.J., served as principal study coordinators. Special thanks to Joseph Fleiss, PhD, Department of Biostatistics, School of Public Health, R.L. Sacco, MD, Department of Neurology, and E. Flaster, MS, Columbia University Computer Center, for advice and assistance in data analysis; to Drs. K.B. Kashkin, N.M. Kurtz, and M. Seligman of Miles Inc. and to D. Tettenborn of Bayer AG for advice on and access to further information on nimodipine; and to all of the above for advice in manuscript preparation.

References

1. Faden AI, Jacobs TP, Smith MT: Evaluation of the calcium channel antagonist nimodipine in experimental spinal cord ischemia. /Neurosurg 1984;60:796-799
13. Lavori P: Comments on repeated measures. Arch Gen Psychiatry 1990;47:775–778

KEY WORDS • cerebral ischemia • clinical trials • nimodipine

Stroke. 1992;23:3-8
doi: 10.1161/01.STR.23.1.3

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/23/1/3