Effect of Intravenous Nimodipine on Blood Pressure and Outcome After Acute Stroke

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Background and Purpose—The Intravenous Nimodipine West European Stroke Trial (INWEST) found a correlation between nimodipine-induced reduction in blood pressure (BP) and an unfavorable outcome in acute stroke. We sought to confirm this correlation with and without adjustment for prognostic variables and to investigate outcome in subgroups with increasing levels of BP reduction.

Methods—Patients with a clinical diagnosis of ischemic stroke (within 24 hours) were consecutively allocated to receive placebo (n=100), 1 mg/h (low-dose) nimodipine (n=101), or 2 mg/h (high-dose) nimodipine (n=94). The correlation between average BP change during the first 2 days and the outcome at day 21 was analyzed.

Results—Two hundred sixty-five patients were included in this analysis (n=92, 93, and 80 for placebo, low dose, and high dose, respectively). Nimodipine treatment resulted in a statistically significant reduction in systolic BP (SBP) and diastolic BP (DBP) from baseline compared with placebo during the first few days. In multivariate analysis, a significant correlation between DBP reduction and worsening of the neurological score was found for the high-dose group (β=0.49, P=0.048). Patients with a DBP reduction of ≥20% in the high-dose group had a significantly increased adjusted OR for the compound outcome variable death or dependency (Barthel Index <60) (n/N=25/26, OR 10.16, 95% CI 1.02 to 101.74) and death alone (n/N=9/26, OR 4.336, 95% CI 1.131 16.619) compared with all placebo patients (n/N=62/92 and 14/92, respectively). There was no correlation between SBP change and outcome.

Conclusions—DBP, but not SBP, reduction was associated with neurological worsening after the intravenous administration of high-dose nimodipine after acute stroke. For low-dose nimodipine, the results were not conclusive. These results do not confirm or exclude a neuroprotective property of nimodipine. (Stroke. 2000;31:1250-1255.)

Key Words: blood pressure • cerebral ischemia • nimodipine • stroke, acute

A n elevated blood pressure (BP) in patients with acute stroke on admission to the hospital is a frequent observation that has been attributed to a multitude of factors. This increased BP usually declines during the first few days.1–6 Although the general recommendation is to not treat a moderate elevation in BP during the first few days,7,8 the issue is not entirely clarified.9,10 In a feline middle cerebral artery occlusion model, pharmacologically induced reduction in mean arterial BP (MAP) causes a parallel change of the regional cerebral blood flow (CBF) in the ischemic portion of the brain.11 In subhuman primates, CBF decreases due to rapidly induced hypotension and hypertensives are more susceptible to cerebral ischemia than are hypotensives.12 In humans, it is suggested that sudden lowering of the BP in the acute stage of occlusive stroke may reduce the cerebral perfusion pressure in the ischemic portion of the brain and increase the chance of irreversible damage,9 although evidence from randomized clinical trials is lacking. Other problems related to BP variations in acute stroke are altered autoregulation of CBF and watershed infarctions after hypertensive therapy.9,13

The Intravenous Nimodipine West European Stroke Trial (INWEST) was conducted to evaluate whether intravenously administered nimodipine, an L-type calcium channel antagonist, improved neurological and functional outcome in acute stroke. The study was terminated after inclusion of about half (n=295) of the planned number (n=600) of patients with acute ischemic stroke patients of indications of neurological worsening after intravenous infusion of nimodipine (1 or 2 mg/h).14 The authors found a correlation between nimodipine-induced reduction in BP and unfavorable outcome. The trial design of INWEST was based on the early positive results of oral nimodipine in acute ischemic stroke15,16 and a positron emission tomography study17 of intravenously administered nimodipine, which indicated a statistically significant beneficial effect on long-term recovery in patients with acute ischemic stroke. Like other calcium channel blockers, nimodipine has an antihypertensive property, and one of its main mechanisms of action is vasodilatation, causing decreased peripheral vascular resistance.18 In previous studies of intravenous nimodipine in patients with...
acute stroke, it was noted that the drug produces hypotension, although no analysis was performed in relation to outcome.\textsuperscript{19,20} The aim of the present study was to confirm the association between nimodipine-induced lowering of BP and outcome after acute stroke with and without adjustment for several prognostic variables and to investigate the outcome in subgroups of patients with increasing levels of BP reduction.

Subjects and Methods
A complete description of the subjects and methods is given elsewhere\textsuperscript{14}; a short summary is given here. A total of 295 patients were enrolled. Ethics committee approval was obtained at each study center, and all patients or their representatives gave informed consent. Patients with a clinical diagnosis of a recent (within 24 hours) ischemic stroke in the carotid artery territory were eligible for inclusion in the trial if they were $\geq$40 years old and functionally independent before the stroke.

Treatment Regimens
Patients received intravenous treatment for 5 days, followed by oral treatment for an additional 16 days. The treatment alternatives were 1 or 2 mg/h nimodipine IV or placebo, followed by an oral dose of 30 mg nimodipine QID or placebo. Patients were consecutively allocated to 1 of the 3 treatments in a double-blind manner.

Definitions
“Average BP” (mm Hg) was defined as the mean value of BP measurements for each day. BP was measured every hour for the first 4 hours, every 4 hours for the next 44 hours, twice daily (morning and evening) for the next 7 days, and then daily while the subject remained in the hospital. “Baseline BP” was defined by BP value just before entering into the study.

BP changes, including systolic BP (SBP) and diastolic BP (DBP) changes, were calculated according to the formula \( [(\text{average BP for each day} - \text{baseline BP})/\text{baseline BP}] \times 100 \).\textsuperscript{17} Orgogozo scores\textsuperscript{21} and Barthel Index scores\textsuperscript{22} were transformed to adjust for the baseline differences, according to a procedure that is described elsewhere.\textsuperscript{15} The transformed score ranged from $-100$ (maximal worsening) to $+100$ (maximal improvements). Patients who died were given a score of $-110$.

“Death or dependency” was defined by Barthel Index score of $<60$.\textsuperscript{23} “MAP” was defined as DBP+$\frac{1}{3}$ (SBP–DBP). “Pulsatility” was defined by (SBP–DBP)/MAP. “New cardiac manifestation” was defined by new ECG abnormality compared with baseline or any cardiac adverse event or cardiac cause of death (clinical or autopsy) during the treatment period.

Statistical Methods
In accordance with the INWEST study protocol, the primary outcome measure was the transformed Orgogozo Score and the transformed Barthel Index score on the follow-up at day 21. The results at week 24 were defined as the secondary outcome. For patients who could not be followed up for any reason, the last available score was carried forward. Statistical comparison to test differences between groups were performed with ANOVA, after validation for normal distribution by use of the Shapiro-Wilk W tests.\textsuperscript{24} The procedure proposed by Bonferroni was used to control multiplicity.\textsuperscript{24} To evaluate the hypothesis of variables in contingency tables, the chi$^2$ test was used or, in the case of small-expected frequencies, Fisher’s exact test. The Spearman rank order correlation coefficient was used to test the hypothesis of independence of variables. In addition to that, descriptive statistical and graphic methods were used to characterize the data. The significance level for statistical testing was taken as \(P<0.05\). Probability value should be regarded as descriptive. The study used multiple hypotheses testing, in which each hypothesis was analyzed separately and the existence of patterns in and the consistency of the results were considered in the analysis. Repeated measurement analysis was used to analyze time-dependent data, and the prognostic power of the different variables was compared with multiple regression analysis. Peto methods\textsuperscript{25} were used to calculate the OR and 95% CI for unadjusted data, and multiple logistic regression analysis were performed to adjust for other prognostic factors. Analyses were carried out by use of SAS and Statistica software.

Results

Recruitment and Baseline Characteristics
Of the 295 patients recruited for the INWEST, 100 were allocated to receive placebo, 101 to receive 1 mg/h nimodipine (low dose), and 94 to receive 2 mg/h nimodipine (high dose). For evaluation of efficacy, 228 patients who fulfilled the validation criteria were included. In this follow-up analysis, 265 patients were eligible for evaluation of the effect of intravenous nimodipine on BP and outcome (92, 93, and 80 in placebo, low-dose, and high-dose groups, respectively). Patients with cerebral hemorrhage (n=15), serious infection or other life-threatening concurrent illness (n=6), no CT scan or no autopsy performed (n=6), BP value overdue (n=2), and delayed inclusion (n=1) were excluded. Some additional patients were accepted for the present but not for the efficacy analysis; these were patients who discontinued treatment for reasons other than death, earlier than 14 days, or temporarily for >1 day, because most of these treatment interruptions were caused by hypotension. There were no statistically significant differences in baseline characteristics and stroke severity between treatment groups.

Nimodipine Titration Rate and Concomitant Hypotensive Medications
Patients in the low-dose group received an average of 0.957 mg/h nimodipine (95% CI 0.935 to 0.979), and those in the high-dose group received an average of 1.82 mg/h nimodipine (95% CI 1.747 to 1.897). The median number of titration rate changes (median 2) was equal in all treatment groups. One hundred seven (40.4%) patients received some kind of antihypertensive medication before randomization (before and after hospital admission). There were 38 (41.3%) patients in the placebo group and 37 (39.8%) and 32 (40%) patients in the low- and high-dose groups, respectively. One hundred twenty-seven patients (47.9%) received at least 1 dose of antihypertensive medication before or after randomization until the end of intravenous treatment period. The distribution was 49 (53.3%) in the placebo and 41 (44.1%) and 37 (46.3%) in the low- and high-dose groups, respectively. The difference between the treatment groups was not statistically significant.

Effect of Nimodipine on BP
The BP course (in mm Hg) and the BP change (%) pattern from baseline are illustrated in Figures 1A and 1B, respectively. Average SBP during the first 2 days (48 hours) was reduced by 2.1% from baseline with placebo, 6.6% with the low-dose \(P=0.008\) versus placebo), and 11.4% with the high-dose nimodipine treatment \(P<0.001\) versus placebo). Average DBP during the first 2 days (48 hours) was reduced by 1.7% with placebo, 7.7% with the low-dose \(P=0.005\) versus placebo), and 14.1% with the high-dose nimodipine
treatment ($P<0.001$ versus placebo). The average pulsatility during the first 48 hours was significantly higher in the low-dose (pulsatility 0.221, $P<0.001$) and the high-dose (pulsatility 0.224, $P<0.001$) groups compared with the placebo group (pulsatility 0.201).

Correlation Between BP Change and Outcome
In Spearman’s correlation analyses, average DBP change from baseline (%) during the first 2 days was significantly correlated to transformed Orgogozo score for all patients at the day 21 ($r=0.14$, $P=0.02$) and the week 24 ($r=0.13$, $P=0.04$) follow-ups. In groupwise analyses, a significant correlation between these variables was found for the high-dose group at day 21 ($r=0.34$, $P=0.002$) and at week 24 ($r=0.23$, $P=0.04$). There was no significant correlation for all patients or in any treatment group between DBP change and transformed Barthel index score at any follow-up except in the high-dose group at week 24 ($r=0.26$, $P=0.02$).

Multiple regression analyses were performed to confirm the findings in Spearman’s correlation analyses. Items included in the analysis were age, sex, history of hypertension, diabetes mellitus or ischemic heart disease (IHD), baseline severity of stroke, baseline BP, SBP and DBP changes during the first 2 days, DBP drop at least once down to ≤60 mm Hg during intravenous treatment, concomitant antihypertensive medications (before or after randomization until the end of intravenous treatment period), and new cardiac manifestations after start of the treatment. For all groups of patients combined, the association between DBP change and transformed Orgogozo score was no longer significant in any follow-up. In groupwise multivariate analysis, a significant correlation between DBP change and outcome at day 21 was found for the high-dose group in terms of both transformed Orgogozo score (standardized $β=0.49$, $P=0.048$) and transformed Barthel index score (standardized $β=0.27$, $P=0.033$). There was no significant correlation between DBP change and outcome in the placebo or low-dose groups or between SBP change and outcome in any group. DBP change was not significantly associated with any outcome measurement at week 24 in multiple regression models. Baseline severity, age, and history of diabetes were findings related to outcome in some analyses. DBP drop down at least once to ≤60 mm Hg was significantly associated with both outcome measures at day 21 in the low-dose group. One hundred thirty-eight (52.1%) patients had experienced DBP drop down to ≤60 mm Hg at least once during the intravenous treatment period. The distribution was 35 (38%), 55 (59.1%), and 48 (60%) in the placebo, low-dose, and high-dose groups, respectively. The difference between the groups was statistically significant ($P=0.004$). Concomitant medication with hypotensive drugs or history of IHD was not significantly associated with outcome.

Outcome in Different Subgroup of Patients According to the Degree of DBP Change
Based on the correlation evidence between DBP change and outcome, DBP change rather than SBP change was selected for the further analysis. The patients were divided into 4 subgroups according to the amplitude of DBP change: sub-

Figure 1. A, SBP and DBP (in mm Hg) course from entry to day 5. D0 indicates entry or baseline; D1, D2, D3, D4, and D5, mean values of day 1, 2, 3, 4, and 5, respectively. B, SBP and DBP changes (%) from baseline during day 1 to 5. Midpoint and top and bottom end of each vertical line represent the mean and upper and lower 95% CI value, respectively.
group 1, no change or increased DBP from baseline; subgroup 2; DBP reduction to \( \leq 10\% \) from baseline; subgroup 3; DBP reduction in \( \leq 10\% \) to \( \leq 20\% \) from baseline; and subgroup 4, DBP reduction in \( \geq 20\% \) from baseline. The unadjusted OR values for death or dependency at day 21 for the nimodipine groups and for each nimodipine-treated subgroup compared with all placebo patients are illustrated in Figure 2. Multiple logistic regression analysis was performed to adjust for age, sex, baseline severity, concomitant antihypertensive agents (including prehospital antihypertensive agents), SBP changes, new cardiac manifestations, and history of hypertension, diabetes, or IHD. The only significant higher OR for death or dependency occurred in the high-dose group with a DBP reduction of \( \geq 20\% \) (OR 10.158, 95% CI 1.02 to 101.735). Case series analysis of the neurological outcome on day 3 in the high-dose nimodipine group revealed a higher incidence of neurological deterioration if average DBP was reduced \( \geq 20\% \) (occurring in 18 of 26 patients) during the first 2 days than in those with a lower degree of DBP reduction (occurring in 18 of 54 patients, \( P \leq 0.005 \)).

Death was analyzed separately. A total of 50 (18.9%) patients were dead at day 21. The distribution was 14 (15.2%) in the placebo group and 20 (21.5%) and 16 (20%) in the low- and high-dose groups, respectively. The difference and adjusted OR between treatment groups was not statistically significant. However, high-dose nimodipine–treated patients with a \( \geq 20\% \) DBP reduction had a mortality rate of 34.6% (9 of 26) and the adjusted OR (4.336, 95% CI 1.131 16.619) was significantly higher compared with placebo at day 21. A comparison of the baseline and demographic data between the subgroups shows no significant difference within the groups, except for age in the high-dose nimodipine group.

**Discussion**

This follow-up analysis confirmed an association between DBP reduction with high-dose intravenous nimodipine and neurological and functional outcome at 21 days after adjustment for several prognostic variables. Unadjusted subgroup analyses indicated that an increase in the OR for death or dependency in the high-dose nimodipine group at day 21 occurred for the moderate-to-profound DBP reduction subgroups (\( \geq 10\% \) reduction). After adjustment for other prognostic factors, the OR for the compound outcome variable death or dependency and for death alone increased significantly for the profound DBP reduction subgroup (\( \geq 20\% \) reduction) treated with high-dose nimodipine. The relationship between DBP reduction and outcome persisted even after adjustment for concomitant antihypertensive medications (including prehospital treatments).

A decrease in BP during the first days after entry occurred in all treatment groups, but the pattern of reduction differed between the placebo group and the 2 nimodipine groups. The gradual decline in BP in the placebo group is known from previous studies and has been attributed to recovery from mental stress due to the emergency and other mechanisms.\(^{1-6}\) There were no significant differences in BP between the treatment groups during the oral phase of the treatment period as reported previously.\(^{14}\) The higher BP reduction in the nimodipine-treated patients compared with the placebo group in this analysis is consistent with previous intravenous and high-dose oral (240 mg/d) nimodipine studies\(^ {3,9,20,26}\) but not with lower-dose oral (\( \leq 120 \text{ mg/d} \)) nimodipine studies.\(^{26-28}\) The difference in BP reduction between the nimodipine groups and the placebo group was more pronounced during the first few days of the intravenous period; thereafter, the difference became successively smaller. This might be due to stabilization of the BP reduction sensitivity by nimodipine with time and continuous decline in the placebo. A reduction in the nimodipine infusion rate in response to hypotensive reactions may contribute to a smaller difference at the end of the intravenous period. Differences in BP between the treat-
ment groups were unintended, and investigators were instructed to reduce the titration rate if the DBP dropped below 50 mm Hg.

While examining the relationship between BP reduction and outcome, we found that DBP reduction was related to outcome in the high-dose nimodipine group but not in the placebo or low-dose group or for SBP in any group. Because both SBP and DBP were reduced in all 3 groups, the relative effect of nimodipine on DBP and SBP can be illustrated by observing the pulsatility of BP, as defined in Methods. A higher pulsatility from the baseline value in the nimodipine-treated groups indicated a greater reducing effect of nimodipine on DBP compared with SBP. The interpretation is that the impact of nimodipine was greater on DBP than on SBP, suggesting a lowering of peripheral resistance, which is a phenomenon related to DBP reduction. Placebo- and nimodipine-treated patients consequently seemed to differ in the BP decrease pattern. In contrast, BP reduction after the relief of mental stress does not seem to be associated with neurological worsening. In the entire group of patients, the correlation between DBP reduction and neurological deterioration may be less prominent after adjustment for prognostic variables than in the nimodipine-treatment groups considered separately.

When the regression analysis was repeated after adjustment for other prognostic variables at 24 weeks, the results were no longer statistically significant, even in the high-dose group. The likely explanation is that the relative effect of BP reduction was more profound early after the stroke and that with time, other unknown factors that were not considered in the study protocol added to both neurological and functional outcome. To prove an association between DBP reduction and outcome even at the late follow-up, a large sample size might be necessary.

In ischemic stroke, the development of infarction and, consequently, outcome is critically correlated to residual perfusion and oxygen availability. Regional CBF is more directly related to systemic BP during the first few weeks after stroke due to the failure of cerebral autoregulation. A reduction in the systemic BP in acute occlusive stroke may risk depriving the patient of the compensatory blood flow through collateral arterial pathways over the surface of brain. Profound hypotension in patients with acute stroke with altered autoregulation may cause a further reduction in cerebral perfusion pressure and a decrease in regional CBF below the lethal thresholds in the penumbra. It is likely that the nimodipine-induced reduction in the BP resulted in deterioration of this collateral supply and may have led to irreversible cell damage. The results of 2 small studies with calcium channel blockers in patients with acute stroke support our hypothesis and show that calcium channel blockers may cause an excessive fall of BP and impair CBF. Cardiac perfusion is determined by DBP, and a very low DBP may induce cardiac ischemia. A potential mechanism for the clinical deterioration with nimodipine in the present study might have been that a low DBP, which is more frequent after nimodipine treatment, resulted in an increased risk for cardiac ischemia. Our results did not support this hypothesis. However, a DBP drop to ≤60 mm Hg was associated with a bad outcome in the low-dose group.

The first 2 days of average BP change were selected for analysis of neurological and functional outcome because the BP difference between the treatment groups was profound in this period. It was also a reasonable decision from a pathophysiological aspect, because ischemia is reversible only for a few hours up to about 24 hours. After 48 hours, reversible ischemia is not likely to occur. In the subgroup analysis of DBP change, all placebo-treated patients were considered as the control group because the placebo group consisted of patients with a natural decline in BP. The baseline characteristics and mechanism of BP reduction in placebo-treated subgroups were not comparable to the corresponding nimodipine-treated subgroups. A higher susceptibility for BP reductions among the elderly patients could be one of the explanations for the imbalance in age between subgroups.

In conclusion, DBP, but not SBP, reduction was associated with neurological and functional worsening on high-dose nimodipine after acute stroke. A profound initial DBP reduction (≥20%) by high-dose nimodipine was associated with increased odds for the compound outcome of death or dependency and of death alone. For slight-to-moderate DBP reduction (<20%) by high-dose nimodipine and for any DBP reduction by low-dose nimodipine, the results were not conclusive. On the basis of this analysis, we were unable to reject or confirm whether nimodipine has a neuroprotective effect in general in patient with acute stroke; we could only determine that in patients treated with high-dose intravenous nimodipine leading to a profound DBP reduction, any neuroprotective effect seemed to be outweighed by the hemodynamic effect. For a final evaluation of a neuroprotective effect of nimodipine in acute stroke, a large study would be necessary; such a trial should exclude the administration of high-dose intravenous nimodipine leading to sudden DBP reduction in 20% or even 10% or more during treatment. A combined treatment with a plasma-expanding drug could be one way to reduce the risk of sudden initial BP reactions.

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