Clinical Trial of a Calcium Channel Blocker in Patients with Aneurysmal Subarachnoid Hemorrhage—Prevention of Delayed Ischemic Deficits

Kyu-Sung Lee, Kyu-Chang Lee and Joong-Uhn Choi

Fifty-three patients with aneurysmal subarachnoid hemorrhage entered a nimodipine trial in the Department of Neurosurgery, Yonsei university to determine the efficacy of the drug in preventing vasospasm and to evaluate the tolerability of this calcium channel blocker. Thirty-three patients completed the study. Treatment was started within four days of initial bleeding and continued for two weeks. Delayed neurological deficits developed in seven of the 33 patients—four from vasospasm, two from elevated intracranial pressure, and one from recurrent bleeding. The incidence of symptomatic vasospasm which developed after calcium channel blocker (nimodipine) treatment was 12.1%, which is about one third of the rate experienced at our department during the past five years (33.2%). Twenty-five patients were operated on without surgical mortality and the morbidity rate was 8%. Side effects due to nimodipine treatment were reversible and insignificant. This study suggests that treatment with a calcium channel blocker that has a selective cerebrovascular effect may prevent or reduce the incidence of delayed ischemic deficits in patients with aneurysmal subarachnoid hemorrhage.

Key Words: Cerebral aneurysm, subarachnoid hemorrhage, vasospasm, calcium channel blocker, nimodipine.

Cerebral arterial spasm is an important complicating factor in patients with subarachnoid hemorrhage following rupture of an intracranial aneurysm. The patient who survives the initial bleeding remains at risk during the next three weeks due to cerebral vasospasm. Vasospasm usually occurs between the third and fourteenth day after a subarachnoid hemorrhage with a peak incidence around the eighth day. Cerebral vasospasm is rarely encountered in conditions other than a subarachnoid hemorrhage resulting from a ruptured aneurysm. Vasospasm increases cerebral vascular resistance and reduces regional cerebral blood flow, which causes ischemic neurologic deficits (Allen et al. 1983; Auer 1984). Cerebral vasospasm is defined as: (a) an angiographic narrowing of the lumen of major cerebral arteries (angiographic vasospasm), (b) the delayed onset of a neurological deficit, (c) the combination of these two features (symptomatic vasospasm). Incidence of angiographic vasospasm differs according to the time of angiography (Taneda 1982). However, symptomatic vasospasm develops in about 30% of the patients with ruptured aneurysm. About half of the patients who experience symptomatic vasospasm eventually die or become severely disabled due to delayed neurologic deficits. The etiology and pathogenesis of cerebral vasospasm are not well understood, and there is no animal model which duplicates all of the key aspects of human cerebral vasospasm. Therefore, most attempts to prevent or treat this condition have failed (Wilkins 1986).

The objective of this prospective clinical trial of nimodipine were to test its effectiveness in preventing or altering the severity of ischemic neurologic deficits due to cerebral vasospasm, and to evaluate the tolerability of intravenously or orally administered nimodipine. The results of this study show that nimodipine significantly reduce the occurrence of severe neurologic deficits from cerebral vasospasm.

MATERIALS AND METHODS

A prospective clinical trial of nimodipine was done on patients admitted to the Department of
Neurosurgery at Yonsei University, with an aneurysmal subarachnoid hemorrhage between March, 1985 and February, 1986. Determination of entry criteria, evaluation of patients during treatment, medical and surgical treatment, and outcome criteria were predetermined and specified in a protocol manual.

1. Patients
   1) Inclusion criteria
      a) age between 15 and 75 years
      b) nimodipine treatment started within 96 hours of initial subarachnoid hemorrhage
      c) patient in clinical grades I to III according to the Hunt and Hess grading system
      d) no ischemic neurological deficit just before the initiation of treatment
      e) documentation of subarachnoid hemorrhage by CT scan or lumbar puncture and/or demonstration of an intracranial aneurysm by an angiography.
   2) Exclusion criteria
      a) pregnancy
      b) severe renal or hepatic insufficiency
      c) cardiac arrhythmia or cardiac decompensation state
      d) intracerebral hematoma with midline shift
      e) generalized cerebral edema
      f) elevated intracranial pressure
      g) concomitant administration of beta-blockers

2. Drug administration
   Patients who were able to swallow tablets were given 240 mg tablets of nimodipine per day in six divided doses at four hour intervals. Nimodipine was administered intravenously to unconscious patients using a volumetric syringe pump (SE 200, Vial Medical, France). A twenty percent nimodipine solution was infused continuously at a rate of 15 mcg/kg/hr for the first two hours. Then the dose was stepped up to 30 mcg/kg/hr if the patient tolerated the trial dose. Nimodipine was topicaly applied to the operating field after clipping the aneurysm. The operating field was bathed with a diluted nimodipine solution (10 mcg/ml nimodipine in Ringer's lactate solution) for a period of ten minutes. The infusion pump and tubes were protected from direct sunlight, as nimodipine is light sensitive, and polyethylene tubing was used because nimodipine is absorbed by PVC tubing.

3. Clinical examination and laboratory tests
   Clinical examinations were performed prior to and during the course of nimodipine treatment, and laboratory tests were done at four to five day intervals.

   Clinical examination involved the following evaluations: physical and neurological condition, state of consciousness according to Glasgow Coma Scale, clinical grade according to Hunt and Hess grade, ECG and vital signs, and CT scan or lumbar puncture.
   Laboratory tests included CBC, ESR, platelet count, electrolytes, blood gases, SMA-12, gamma-GT, and urinalysis.

4. Duration of treatment
   Nimodipine treatment was continued for at least two weeks following the initial hemorrhage. If the patient had surgery during the prophylactic treatment, the intravenous infusion was continued for at least five days after the operation.

5. Evaluation of drug effects and adverse reactions.
   Upon completion of the nimodipine treatment, a detailed neurological examination was done together with laboratory examinations. Treatment outcome was evaluated by Glasgow Outcome Scale. All abnormal findings or subjective symptoms occurring during the study were evaluated in detail and their possible connection with nimodipine treatment was assessed. Patients were excluded from final evaluation if treatment was discontinued before the fourteenth day.

   RESULTS

1. Patients
   Forty-one of the initial 43 patients met the entry criteria. Two patients received nimodipine treatment more than 96 hours after the initial bleeding. Eight of the 41 patients who met the entry criteria were excluded from the analysis, because a 14-day course of nimodipine treatment could not be completed. Five of the eight patients had elevated intracranial pressure, and the remaining three showed increased serum transaminase levels of greater than 100 IU/ml during treatment. the results of nimodipine treatment in the remaining 33 patients were analyzed.

2. Surgical treatment
   1) Patient profile: Twenty-five of the 33 patients underwent aneurysm surgery, while five patients refused surgery, and three others had a primary subarachnoid hemorrhage. Only one of the five patients who declined surgery was in good condition after completion of nimodipine treatment. The four patients who refused surgery were in poor condition; three from vasospasm and one from recurrent bleeding. However, nimodipine treatment was com-
pleted in all eight non-surgical cases.

2) Surgery: Emergency surgery was performed on one patient due to a huge intracerebral hematoma which accompanied the ruptured aneurysm. Three patients were operated on within 48 hours of initial bleeding, while the remaining 21 patients had surgery more than two weeks after the initial bleeding.

The aneurysms were located in the following areas: ten in the anterior communicating artery, six in the posterior communicating artery, five in the middle cerebral artery, and one each in the internal carotid artery, anterior cerebral artery, basilar bifurcation, and posterior inferior cerebellar artery.

3) Results of surgical treatment: The results of the surgery as scored by Glasgow Outcome Scale are summarized in Table 1. There was no surgical mortality. Two patients suffered from major neurologic deficits which were not directly related to the surgery. One patient had a dense hemiparesis as a result of an intracerebral hematoma, and another had a fixed deficit due to preoperative cerebral vasospasm. Four patients displayed transient neurological deficits-two ischemic deficits from vasospasm, one from intracerebral hematoma, and the other from hydrocephalus.

<table>
<thead>
<tr>
<th>Table 1. Outcome of patients</th>
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<tr>
<td>Glasgow Outcome Scale</td>
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<td>-----------------------------</td>
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<tr>
<td>Nimodipine treated patients</td>
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<td>(N=33)</td>
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<td>Operated patients</td>
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<td>(N=25)</td>
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3. Effects of calcium channel blocker (nimodipine)

1) Clinical outcome: The results of nimodipine treatment are summarized in Table 1. Seven of the 33 nimodipine treated patients had major fixed deficits, four of which resulted from cerebral vasospasm. Other causes of deficits included two cases of elevated intracranial pressure and one of recurrent bleeding.

As four of the 33 patients given nimodipine fell into the severe deficit-outcome category due to vasospasm, the incidence of clinical vasospasm in the nimodipine treated group was 12.1%. In our department the incidence of clinical vasospasm was 33.2% prior to the availability of nimodipine treatment, thus nimodipine significantly reduced the number of cases of severe neurologic deficits.

2) Adverse reactions: Ten patients demonstrated a reversible elevation of serum transaminases and gamma-GT during nimodipine treatment. Nimodipine treatment was discontinued in three patients whose SGOT and SGPT levels were increased to more than 100 IU/ml. Transaminase levels returned to normal after the discontinuation of nimodipine. The relationship between the elevation of liver enzyme levels and nimodipine treatment could not be assessed, because a number of medications such as anticonvulsants, anti-hypertensive, antifibrinolytic and analgesics were given concurrently.

Two cases of transient premature ventricular contractions were observed during nimodipine treatment, but these were controlled by intravenous lidocaine injections. Other side reactions occurring during nimodipine treatment included gastrointestinal problems, skin rashes, and fever of unknown origin. Again, the relationship between these reactions and the nimodipine treatment could not be defined.

4. CT findings and outcome

Management outcome decreased in proportion to increase in the amount of hemorrhage in the basal cisterns on the initial brain CT scan. No patient in the mild bleeding group was rated higher than grade 2 on the Glasgow Outcome Scale. In contrast, three of the twenty in the moderate bleeding group (15.0%) and four of the six in the severe bleeding group (66.7%) had major neurologic deficits-higher than grade 3 on Glasgow Outcome Scale.

DISCUSSION

In recent years, there has been great interest in the use of calcium antagonists to prevent or reverse cerebral vasospasm by interfering with intracranial arterial constriction (Kazda and Towart 1982; Petroutka and Allen 1983). To be effective, such drugs must cross the blood brain barrier to reach the cerebral arterial smooth muscle cells, and their antagonistic effect should be selective to cerebral vessels (Allen 1984). Nimodipine, isopropyl (2-methoxy-ethyl) 1,4-dihydro-2,6-di-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate, is a lipid soluble calcium antagonist vasodilator with a preferential effect on cerebral
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vessels. Nimodipine has been shown to have a selective cerebrovascular spasmolytic effect in animal experiments (Kazda et al. 1982; Towart et al. 1982), and to improve the prognosis of a patient with a ruptured aneurysm by reducing the occurrence of delayed ischemic deficits (Auer 1984; Ljunggren et al. 1984).

In an animal study, Kazda et al. (1982) showed that systemic administration of nimodipine dilated cerebral vessels much more than peripheral arteries. Allen (1984) contended that cerebral blood vessels are particularly sensitive to calcium channel blockers, because the influx of extracellular calcium is the primary source of calcium for the contraction of the large cerebral arteries. Kazda and Towart (1982) suggested that different populations of calcium channels exist in the membranes of different vessels, and that the receptor operated channels in brain vessels differ substantially from those of peripheral vessels.

Ljunggren et al. studied outcome in 60 patients treated with early aneurysm surgery and intravenous nimodipine. They concluded that early operative intervention was beneficial in patients in good condition rather than delaying the surgery, and indicated that nimodipine provides an additional anti-ischemic effect (Ljunggren et al. 1982, 1984). Auer (1984) reported on the results of patients with ruptured aneurysms treated by acute operation and preventive nimodipine. Ninety-one percent of his patients who were in grades I to IV preoperatively were in placed in the fair to excellent result groups postoperatively. Only 14% of the patients in grades III or IV had poor prognosis or died. He speculated that the better outcome of patients in his studies as compared to those in recent studies of early surgery was due to the effect of nimodipine. It is also indicated in this study that nimodipine significantly reduces the occurrence of severe neurologic deficits from vasospasm in patients with ruptured aneurysms.

In the authors' prospective study, delayed neurologic deficits from vasospasm developed in four patients (12.1%) which was only one third of the incidence rate (33.2%) experienced by the authors before the nimodipine treatment (Park et al. 1985). The pre-and postoperative regimens as well as the surgical procedures were the same in all aspects, with the exception of the nimodipine treatment when compared to the historical control group (Park et al. 1985). Although the incidence of severe deficits from vasospasm was significantly reduced, 12.1% is higher than in other reported studies. This could be explained by the fact that the outcome of management was estimated immediately after nimodipine treatment or surgery, and that most of the patients in our study were given tablets of nimodipine. It is possible that absorption of orally administered nimodipine is unpredictable and probably lessens the effect of the drug. The mean plasma level of Allen's patients (Allen et al. 1983), who were given half the dose of our patients, was 6.9 ng/ml. Ljunggren et al. (1984) reported that a steady state concentration in the range of 12 to 35 ng/ml during intravenous infusion of nimodipine at a rate of 30 mcg/kg/hr. Auer (1984) also reported that plasma levels of nimodipine were two to three times higher when it was administered intravenously rather than orally. Our study had two limitations. It was impossible to carry out a double blind study because nimodipine was directly supplied from Bayer AG in the Federal Republic of Germany. The other was that the duration of the prospective study was only one year, which seemed to be too short to fully evaluate any delayed effects of the drug and recovery of the patients.

We believe that maintenance of a circulating blood volume and administration of nimodipine, which has a selective effect on cerebral vessels, is the best approach to prevent the occurrence of delayed ischemic deficits from symptomatic vasospasm in patients with ruptured cerebral aneurysms. Further research as to whether or not dihydropyridines exert anti-ischemic effects mediated by other mechanisms is necessary.

REFERENCES


