Poor Utilization of Nimodipine in Aneurysmal Subarachnoid Hemorrhage

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Objective: To determine adherence to nimodipine administration in patients admitted with aneurysmal subarachnoid hemorrhage (aSAH). *Background:* Oral nimodipine (60 mg every 4 hours for 21 days) is recommended by the national guidelines for aSAH. A Cochrane systematic review has determined that nimodipine reduces the risk of cerebral ischemia and is currently the only effective drug for the prevention of vasospasm in aSAH patients. *Design/Methods:* We retrospectively analyzed 109 patients with aSAH admitted to the Neurosciences Intensive Care Unit (NICU) at a tertiary care medical center between 2010 and 2013. Nimodipine-prescribing patterns, days of therapy completed, and adverse effects were tabulated. Patients not initiated on nimodipine and reasons for prematurely stopping therapy were noted. *Results:* One hundred two (93%) patients with aSAH were started on oral nimodipine upon admission to the NICU. Early death (3%) and hypotension (1%) were reasons why patients were not started on nimodipine. Only 36 (33%) patients received nimodipine, 60 mg orally every 4 hours for 21 days. In 26 patients (39%), the dose of nimodipine was reduced because of excessive drops in blood pressure. Transient discontinuation occurred in 2 (2%) patients. Thirty one (47%) patients were discharged from the hospital before 21 days and nimodipine was not ordered to continue at home. *Conclusion:* We found that the majority of patients with aSAH in our practice did not complete 21 days of nimodipine. Hypotension was mostly responsible for dosing change or discontinuation.

Key Words: Aneurysmal subarachnoid hemorrhage—hypotension—nimodipine—medication adherence

Introduction

Cerebral vasospasm and delayed cerebral ischemia are 2 serious complications patients with aneurysmal subarachnoid hemorrhage (aSAH) may encounter during their ICU stay. Pharmaceutical options for preventing these complications are limited. Nimodipine is the only approved pharmacological agent in the United States for preventing delayed cerebral ischemia in aSAH.[1,2] Current evidence supports the oral administration of nimodipine 60 mg every 4 hours for 21 days after aSAH.[3] Nevertheless, despite the cerebral vasodilatory effects of nimodipine, there is no convincing evidence that it reduces the incidence of angiographic vasospasm. However, nimodipine reduces cerebral infarct size and improves neurological outcomes.[4–6]

Nimodipine is a dihydropyridine calcium channel blocker that works primarily on cardiac and vascular smooth muscle fibers preventing vasoconstriction. It is different from other dihydropyridine calcium channel blockers in that, it dilates cerebral arteries to a greater extent than the coronary or peripheral vessels because of its ability to cross the blood-brain barrier. The recommended dose for vasospasm prevention is 60 mg orally every 4 hours for 21 days. One of the more serious side effects of nimodipine is hypotension, which can potentially lead to hypoperfusion and worse neurological outcomes.[7] However, patients with aSAH who cannot tolerate the hypotensive effects of nimodipine will not

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benefit from its anti-inflammatory, neuroprotective[8] and profibrinolytic[9] effects. We reviewed our experience in utilizing nimodipine in patients with aSAH and how the dosing of the drug varied when patients experienced adverse side effects from the medication.

Methods

We retrospectively reviewed full medical records of patients with aSAH, admitted to NICU at a tertiary care medical center between 2010 and 2013. During the ICU stay, patients were monitored closely by hourly neurological assessment by neurosciences intensive care nurses, transcranial Doppler ultrasound, and neuroimaging per hospital protocols. Treatment was in accordance with American Heart Association's Guidelines for the Management of aSAH[1] with an emphasis on the early obliteration of aneurysm with endovascular coiling and/or surgical clipping, blood pressure monitoring, ventricular drainage of cerebrospinal fluid for management of hydrocephalus, oral nimodipine, and maintenance of euvolemia.[10]

Patients with neurological decline attributed to vasospasm were treated with blood pressure augmentation consisting of intravenous fluid administration and vasopressor support. In these patients, vascular imaging using CT angiogram, CT perfusion, or digital subtraction angiogram was obtained per the discretion of neurointensivist. In patients with persistent clinical deterioration despite hemodynamic augmentation and neuroimaging study confirmed vasospasm, selective catheter angiography was done by administration of an intra-arterial calcium channel blocker, such as verapamil. In a selected group of patients who did not respond to an intra-arterial infusion of verapamil, angioplasty was performed per the discretion of neurointerventionist or vascular neurosurgeon.[11]

At our institution, patients with aSAH s are started on nimodipine, 60 mg orally every 4 hours within the first 24 hours of confirmed SAH. If patients experience hypotension with nimodipine administration, doses are often reduced (i.e., 30 mg orally every 2 hours) or withheld until the blood pressure improves. In most cases of hemodynamic augmentation requiring pressors, nimodipine was transiently held. Descriptive statistics were used to summarize the data. All reported *P* values are 2-sided.

Results

Data from 109 patients were analyzed. Baseline and clinical characteristics of patients, grouped according to their nimodipine adherence, are shown in Table 1.

Oral nimodipine was started on 102 (93%) patients with aSAH on. Reasons for not starting patients on nimodipine included early death (3%) and hypotension (1%). Only 36 (33%) patients completed a full course of nimodipine (60 mg every 4 hours for 21 days). Among those who did not complete the full course of nimodipine, a decrease in blood pressure was the reason in 26 (39%) patients. Thirty-one (47%) patients were discharged from the hospital without instructions to complete the course (i.e., medication not listed on the home medication list). In 6 (9%) patients, there was no documented reason for to hold administration of nimodipine, but we suspect blood pressure augmentation may have prompted discontinuation.

In 13 (12%) patients, the dose of nimodipine was changed to 30 mg every to 2 hours because of excessive blood pressure reduction. Only 3 of those patients completed the 21-day course of treatment. Thirty (27%) patients required blood pressure augmentation during the hospitalization with either vasopressor or crystalloid therapy. Only one-third of those patients completed the full course of treatment.

There was no difference in outcome between patients who received the full course of nimodipine and those who did not receive the full course after adjustment for severity of subarachnoid hemorrhage. Patients' WFNS scale did not differ significantly between those who received the 21-day course of nimodipine and those who did not (*P* value = .07). Modified Fisher grades also were not significantly different between the two groups (*P* value = .77; age, based on WFNS score).

Discussion

Our study revealed that many aSAH patients do not receive the full course of oral nimodipine—the only proven prophylaxis for symptomatic cerebral vasospasm. Decrease in blood pressure, which was deemed unacceptable, was the main reason for early discontinuation of therapy.

Nimodipine is dosed every 4 hours, has notable drug-drug interactions with other Cytochrome P450 3A4 medications, and ideally should be administered on an empty stomach.[12] Just recently, nimodipine became available as an enteral solution. Previously if patients could not swallow the liquid-filled capsule, the contents had to be extracted from the gel cap with a needle and syringe and then administered sublingually or through a gastric tube.

Nimodipine causes vasodilation that may lead to hypotension in hemodynamically unstable patients. ICU patients are at further risk for blood pressure-related problems because of changes in enteral nutrition (i.e., being NPO for tests), frequent medication changes, immobility, and infections.

Our results are comparable to a recent study from Germany.[7] In that study, only 43.6% of 270 patients received the full daily dose of nimodipine. In 28.6% of patients, the dose was reduced by 50%, and in 27.7% of patients, the drug was discontinued. That study related poor outcomes to poor compliance; however, this may not always be the case. One limitation of our study may be a very low threshold of holding nimodipine in the event of a blood pressure drop. In patients requiring hemodynamic augmentation, continued administration

Table 1. *Clinical characteristics of patients with SAH*

Variable		21-days nimodipine	
	(n = 109)	Yes (n = 36)	No (n = 73)
Age (year)*	56 ± 12.7	59 ± 13.1	54 ± 12.3
Male Gender (%)	33.0	27.7	35.6
Medical History (%)			
Hypertension	55.0	50	57.5
Smoking	43.5	30.6	50
Diabetes Mellitus	11	16.6	8.6
Median WFNS[†,‖] (Presentation)	2.4	2	2.6
Low grade (1,2) (%)	64.2	75	58.9
High grade (3-5) (%)	35.8	25	41.1
Median WFNS[‖] (Worst)	2.7	2.4	2.8
Low grade (1,2)	52.3	52.8	52
High grade (3-5)	47.7	47.2	48
Median WFNS[‖] (Postresuscitation)	2.1	1.8	2.3
Low grade (1,2)	65.1	75	60.3
High grade (3-5)	34.9	25	39.7
Median Modified Fisher[‖]	3.1	2.9	3.2
DCI[‡,‖](%)	28	18	32
Angiographic Vasospasm[‖](%)	48	37	64
Median mRS[§,‖]	1.9	1.7	2.1
Low mRS (0-2) (%)	60.5	61.1	60.2
High mRS (3-6) (%)	39.5	38.9	39.7

*Plus-minus values are mean ± SD.
[†]World Federation of Neurological Surgeons grading of Subarachnoid Hemorrhage.
[‡]Delayed cerebral ischemia.
[§]modified Rankin Scale.
[‖]None of the differences were statistically significant (Chi-Square, *t* test).

could lead to unnecessary incremental dosing of vasopressors. Our practice has been to transiently hold nimodipine during the cerebral vasospasm period, and this was reflected in the low number of patients on nimodipine who showed angiographic vasospasm. Poor utilization of nimodipine, therefore, requires attention and prospective evaluation.

The outcome in our patients was similar whether or not they completed a full course of nimodipine. However, this retrospective study is insufficient to address the question adequately. Also, nimodipine was discontinued in some patients to improve blood pressure goals and may have skewed the data.

Our findings suggest that current use of nimodipine in aSAH is difficult to implement in clinical settings given the hemodynamic instability of these patients. Further prospective studies are necessary to address this challenge. One consideration would be a prospective study testing maintenance of blood pressure using vasopressors in a low dose without discontinuation of nimodipine. For now, an adequate solution to this major side effect is not known.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.04.024.

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