Pediatric Neurology 52 (2015) 356–360

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Nimodipine for the Prevention of Cerebral Vasospasm After Subarachnoid Hemorrhage in 12 Children

Josh Heffren PharmD [a], **Angela M. McIntosh PharmD, BCPS** [b], **Pamela D. Reiter PharmD** [b,c,*]

[a] *Department of Pharmacy, Seattle Children's Hospital, Seattle, Washington*
[b] *Pediatric Intensive Unit, Department of Pharmacy, Children's Hospital Colorado, Aurora, Colorado*
[c] *Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Anschutz Medical Campus, Aurora, Colorado*

ABSTRACT

INTRODUCTION: Subarachnoid hemorrhage is a rare, but life-threatening neurological emergency. Cerebral vasospasm is a complication of subarachnoid hemorrhage that contributes significantly to morbidity and mortality. Nimodipine has been used in adults to reduce the incidence of cerebral vasospasm after subarachnoid hemorrhage and improve long-term outcomes. There are, however, no data in children. **METHODS:** Records of children with a confirmed diagnosis of subarachnoid hemorrhage who received nimodipine between January 1, 2005 and August 31, 2013 were reviewed. Dosing of nimodipine and associated hypotensive events were recorded. Transcranial Doppler ultrasonography, cranial computerized tomography, and angiography were followed as a measure of cerebral vasospasm, rebleeding, and subsequent infarction. **RESULTS:** Twelve children (average age 11.8 ± 3.3 years, age range 3.5 to 17.3 years) were included. Aneurysm was responsible for the highest percentage (41.7%) of subarachnoid hemorrhage events. The mean dose of oral nimodipine was 1 mg/kg every 4 hours and was associated with a high rate of hypotension requiring intervention or dose modification. Clinical outcomes while on nimodipine therapy varied; evidence of vasospasm was observed in 67%, new infarction in 33%, and rebleeding in 17%. Functional and cognitive deficits were minor in two-thirds and absent in the remaining individuals. All patients survived until hospital discharge. **CONCLUSIONS:** Oral nimodipine after subarachnoid hemorrhage in children does not eliminate vasospasm, rebleeding, or infarction and is associated with significant hypotension. Nevertheless, clinical outcomes appear favorable relative to the adult population who receive nimodipine. Further study, with dose titration, is warranted.

Keywords: pediatric nimodipine dosing, subarachnoid hemorrhage, cerebral vasospasm, cerebral infarction, rebleeding events, aneurysm, arteriovenous malformation

Pediatr Neurol 2015; 52: 356-360

Introduction

Pediatric subarachnoid hemorrhage (SAH) is a rare, yet devastating condition. It can leave those affected with long-term neurological deficits or result in early death. The etiology of SAH in children is multifactorial and includes aneurysms, arteriovenous malformations, tumors, trauma, coagulopathies, and vasculitis. A leading cause of morbidity and mortality after SAH is triggered by cerebral vasospasm leading to infarction and/or recurrent hemorrhage. Cerebral arterial spasm generally occur 3 to 4 days after the SAH, peaking around 6 to 8 days, and can recur for up to 2 to 3 weeks.[1,2] A number of pharmacologic interventions have been proposed to reduce vasospasm, including calcium channel blockers.

Nimodipine is a lipid soluble, dihydropyridine calcium channel blocker that crosses the blood-brain barrier and blocks the influx of extracellular calcium into the vascular smooth muscle cell. It has been studied extensively in adults

The authors declare no conflicts or financial interest in any product or service mentioned in the article, including grants, equipment, medications, employment, gifts, and honoraria.

Article History:
Received July 16, 2014; Accepted in final form November 5, 2014

* Communications should be addressed to: Dr. Reiter; Pediatric Intensive Unit; Department of Pharmacy; Children's Hospital Colorado; 13123 East 16th Ave; Aurora, Colorado.
E-mail address: pam.reiter@childrenscolorado.org

0887-8994/$ - see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.11.003

with SAH at risk for vasospasm and is currently the only calcium channel blocker with a US Food and Drug Administration indication for cerebral vasospasm management. It has been shown to improve neurological recovery and decrease cerebral infarction, symptomatic vasospasm, and mortality.[3] Therefore, in an effort to prevent delayed cerebral ischemia, nimodipine (60 mg orally every 4 hours for 3 weeks) is currently regarded as the standard of care in adults after SAH.[4] Data in children, however, are not readily available. Therefore, we describe the treatment of cerebral vasospasm in children following multiple etiologies of SAH. We will also report clinical outcomes associated with therapy, including rebleeding episodes, incidence of vasospasm, evidence of cerebral infarction, cognitive function, and mortality.

Methods and Main Results

This was an institutional review board approved, retrospective, electronic medical record review of children (31 days through 18 years of age) with a confirmed diagnosis of SAH who received nimodipine for prevention or treatment of vasospasm between January 1, 2005, and August 31, 2013. Because of an anticipated low number of subjects (given the rarity of the disease state), we limited our exclusion criteria to maximize our sample size. These exclusion criteria involved the neonatal population and pregnant females. However, neither was identified during the review. Quantitative variables are described using measures of central tendency (mean, median, standard deviation, range). Qualitative or categorical data are described as frequency and percentage. Student *t* test was performed to detect any statistical differences in outcome variables. A *P* value of <0.05 was considered statistically significant.

A total of 16 patients met initial review criteria; four were excluded because they were transferred to another hospital shortly after diagnosis and were lost to follow-up, leaving a total of 12 patients for analysis. These patients (age = 11.8 ± 3.3 years (3.5-17.3); weight = 42.2 ± 16.3 kg (15-71.4); 67% male) experienced a SAH from a variety of etiologies, Table 1. All children were admitted directly to the pediatric intensive care unit and received care by the neurosurgical and critical care services. The highest percentage of patients experienced SAH secondary to aneurysm. Before initiation of nimodipine, vasospasm was identified (via cerebral angiography) in two children and infarction (via computerized tomography [CT]) was detected in three children. Most patients (58%, n = 7) received concomitant therapies for vasospasm (magnesium, n = 2; magnesium plus simvastatin, n = 5). Most patients (n = 10) received their first nimodipine dose within 96 hours of presentation, Table 2. The mean starting dose was approximately 1 mg/kg orally every 4 hours and, in spite of half of the patients requiring some dosing regimen modification during hospitalization, the ending dose was very similar.

Hypotension was defined by the attending neurosurgeon and in most instances correlated with a systolic blood pressure <90 mm Hg. There were 77 documented hypotensive events during treatment with nimodipine. These events occurred among 10 patients. Fifty events required administration of fluids (normal saline bolus), 48 events resulted in a held dose of nimodipine, and 10 events resulted in a dose adjustment. One patient had therapy discontinued after 4 days because of hypotension. Because magnesium sulfate administration can also result in hypotension, we compared the number of hypotensive events per patient between those receiving nimodipine alone (n = 5) and those who received concomitant magnesium (n = 7). No significant relationship was detected, with 9.8 ± 10.8 and 8.6 ± 5.2 events per patient in the groups, respectively (two-tailed *T* test, $P = 0.80$). The average daily dose of nimodipine was higher among patients experiencing hypotension that required intervention versus those who did not require intervention (6.3 ± 2.7 mg/kg/day versus 5.1 ± 3.9 mg/kg/day), but this was not statistically significant (two-tailed *T* test, $P = 0.46$).

Nine children had transcranial Doppler ultrasounds performed to determine presence of vasospasm. Eighty-nine percent of those children (n = 8) had evidence of cerebral vasospasm; one had episodes of moderate-severe vasospasm (blood flow velocity >200 cm/s), three had episodes of mild vasospasm (blood flow velocity, 160-199 cm/s), and four had evidence of both. All patients with severe vasospasm had subsequent evidence of restricted diffusion, consistent with ischemia. Although the daily nimodipine dose was lower in those children who experienced a vasospasm (5.2 ± 2.3 mg/kg/day vs 8.5 ± 4.9 mg/kg/day), the difference did not meet statistical significance (two-tailed *T* test, $P = 0.25$). Clinical outcomes varied among children, Table 3. A total of five children remained infarction free throughout the course of nimodipine therapy, three children had evidence of infarction before nimodipine initiation, and four children developed infarction on therapy. Seventeen percent of patients (n = 2) had evidence of rebleeding on CT scan while on nimodipine therapy. Most patients (9 of 12) had some type of surgical intervention performed after initial identification of the SAH (Table 3). Minor functional or cognitive deficits were present in 67% of children at discharge. The remaining 33% were discharged without evidence of

TABLE 1.
Demographic and Clinical Features of 12 Children who Received Nimodipine After Subarachnoid Hemorrhage (SAH)

Patient Number	Weight (kg)	Age (yr)	Gender	Etiology of SAH	Initial Oral Nimodipine Regimen	Duration of Nimodipine (days)	Intervention Required for Hypotension During Therapy
1	36	12.3	Female	Arteriovenous malformation	30 mg q2h	25	One fluid bolus, 24 held doses, one dose modification
2	40	11.3	Male	Aneurysm	30 mg q2h	18	Eleven held doses and two dose modifications
3	29.5	10.4	Male	Trauma	30 mg q4h	21	Eight fluid boluses and two dose modifications
4	42.1	13.6	Male	Aneurysm	30 mg q4h	4	Two fluid boluses, six held doses and eventual early therapy discontinuation
5	15	3.5	Male	Arteriovenous malformation	30 mg q4h	21	None
6	52.5	12.9	Male	Undetermined	60 mg q8h	46	None
7	71.4	17.3	Female	Aneurysm	30 mg q4h	21	Seventeen fluid boluses
8	27.9	9.4	Male	Trauma	60 mg q4h	19	Four fluid boluses and one dose modification
9	32.4	12.1	Male	Aneurysm	15 mg q2h	25	One fluid bolus and four held doses
10	66.4	14	Male	Undetermined	60 mg q4h	36	Two fluid boluses
11	39.5	10.9	Female	Cavernous sinus thrombosis, bleeding disorder	30 mg q4h	13	Four fluid boluses, two held doses, and three dose modifications
12	53.5	13.5	Female	Aneurysm	30 mg q4h	21	Eleven fluid boluses, one held dose, and one dose modification