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Safety of Nimodipine in Critically Ill Aneurysmal Subarachnoid Hemorrhage Patients

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Abstract

Background: Nimodipine Oral Capsules (NOC) and Oral Solution (NOS) are used to prevent delayed cerebral ischemia in patients following an aneurysmal subarachnoid hemorrhage (aSAH). Due to increased reports of diarrhea with NOS, Virginia Commonwealth University Health (VCUH) now uses NOC and compounded oral syringes for dose administration. This study evaluates the safety of NOC and NOS in the treatment of critically ill aSAH patients admitted to the Intensive Care Unit.

Methods: A retrospective chart review was performed for aSAH patients receiving NOC or NOS from June 1, 2013 to December 31, 2015 to evaluate the incidence of adverse drug reactions (ADRs) for NOS and NOC, including diarrhea, decreases in Systolic Blood Pressure (SBP), and SBP-associated nimodipine dosage adjustments.

Results: Of patients receiving NOS, 82% experienced diarrhea compared to 52% who received NOC (p=0.02). Of the 69 patients who experienced diarrhea, 94% received at least one agent that is commonly associated with diarrhea. Overall, 92.7% of NOC patients experienced a median SBP reduction of 35 mmHg compared to 22 mm Hg receiving NOS (p=0.06). Doses were decreased from 60 mg to 30 mg in 61% of NOC patients versus 24% of NOS patients (p= 0.18).

Conclusion: Critically ill aSAH patients receiving NOS were more likely to develop diarrhea compared to those receiving NOC. Most patients experiencing diarrhea received at least one concomitant medication associated with diarrhea. There was a clinically significant reduction in median SBP observed for both formulations and a majority of patients required dosage adjustments.

Keywords: Nimodipine; Nymalize; Aneurysmal Subarachnoid Hemorrhage; Diarrhea; Hypotension; Adverse Effect

Key Points

1. Patients who receive nimodipine oral solution are at increased risk of experiencing diarrhea compared to those receiving the oral capsules.
2. Adverse effects associated with nimodipine therapy, such as diarrhea and hypotension, may contribute to poor patient outcomes and increased healthcare costs.
3. When assessing the cost-effectiveness of nimodipine formulations, institutions should carefully balance cost savings with patient safety, health outcomes, and overall healthcare expenditure.
4. The inconsistent medication safety profile across nimodipine formulations should play a key role in determining an appropriate therapeutic regimen as new formulations are approved.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) affects approximately 300,000 people in the United States each year [1]. Complications that may arise following aSAH include delayed cerebral ischemia and rebleeding, which are associated with an increased risk of mortality and poor prognosis for functional recovery [1]. Delayed cerebral ischemia of the cerebral arteries occurs in 12-30% of patients following an aSAH [2]. Nimodipine, a dihydropyridine calcium channel blocker, prevents contraction of smooth muscle and is the only treatment shown to be efficacious in preventing delayed cerebral ischemia [3]. The current standard of care globally is to initiate nimodipine therapy at the time of hospital admission and continue for up to 21 days after rupture [4].

Nimodipine Oral Capsules (NOC) were initially FDA-approved in December 1988 with generic formulations brought to market in 2007. In aSAH patients requiring feeding tube placement for enteral feeding and medication administration during hospitalization, the contents of the soft gel NOC have to be drawn up into a syringe by a nurse or pharmacy technician for administration via the feeding tube. These compounded oral syringes serve as an alternative administration strategy but create many safety concerns. One of the most serious issues has been administration errors, with several reports of intravenous administration of the nimodipine compounded oral syringes to the FDA Adverse Event Reporting System (AERS) and the Institute for Safe Medication Practices (ISMP) [5]. The FDA responded in 2006 by adding a boxed warning against the intravenous administration of nimodipine and added specific instructions for compounding syringes for oral administration [6]. As a result of these safety events, the FDA approved Nymalize®, a 30 mg per 10 mL nimodipine oral solution (NOS), in 2013 as an alternative formulation for patients unable to use the oral capsules.

The NOS formulation offers a more convenient method of administration for patients with feeding tubes, provides consistent liquid dosing, reduces compounding time, and minimizes the possibility of administration errors. The safety profile and adverse events reported by the manufacturer for NOS are the same as those reported for NOC [6]. However, anecdotal data suggest that NOS may be associated with an increased risk of diarrhea and more significant blood pressure lowering compared to the oral capsules.

When our institution switched its preferred product to the NOS in 2013, nurses reported an increase in the incidence of diarrhea in patients being treated for aSAH and receiving NOS. Diarrhea is a known side effect of nimodipine that occurs in 3% of patients [7]. However, it is not known if the NOC and NOS formulations carry the same risk of diarrhea. Patients who acquire nosocomial diarrhea are hospitalized for longer periods, are at an increased risk of exposure to other hospital infections and have a higher mortality rate than patients without diarrhea [8]. It is hypothesized that diarrhea may precipitate from polyethylene glycol, an ingredient found in the manufactured oral solution, but the exact mechanism is unknown.

Another common adverse effect of nimodipine is hypotension. An analysis of four clinical trials found that 5% of patients treated with NOS experienced a drop in blood pressure compared to 1% of patients receiving placebo [7]. This resulted in more complex management of these patients, discontinuation of the NOS, and a return to the manual compounding of oral syringes from nimodipine capsules. Hypotension following aSAH may have a detrimental effect on patient outcomes and the extent of blood pressure lowering and patient outcomes between nimodipine formulations have yet to be evaluated.

To date, there are no studies comparing the safety profiles of NOS and NOC in the treatment of patients with aSAH. This study was conducted to evaluate the safety of NOC versus NOS in the treatment of aSAH patients, as measured by the incidence of diarrhea and blood pressure lowering adverse events.

Methods

This retrospective study evaluated aSAH patients receiving nimodipine who were admitted to the Virginia Commonwealth University Health (VCUH) neurosurgery service between June 1, 2013 and December 31, 2015. The study was determined to qualify for exemption by the VCUH Institutional Review Board (IRB) and data was retrieved from the electronic medical record. Adult patients aged 18 to 89 years old who were treated with either NOC, including whole capsules and those compounded into oral syringes, or NOS were included in the study. Patients were included in the NOS group if they received at least one dose of NOS during the treatment course. Patients were excluded if they were prisoners, pregnant, had a diagnosis of chronic diarrhea, or had a hospital length of stay less than or equal to two days. The primary objective of this study was to evaluate the safety of NOC versus NOS following aSAH as measured by the incidence of diarrhea and hypotensive events in neurocritical care patients. The secondary objective was to evaluate the concomitant effect of laxatives, antibiotics, and enteral nutrition on the incidence of diarrhea in patients receiving NOC and NOS.

Patient characteristics and injury diagnosis codes were collected. Treatment-specific data included the nimodipine formulation administered, dose, time of administration, and dose adjustments made at any point during therapy. Safety data included the day and time of the diarrhea occurrence, documented as loose, watery, or liquid stool in the patient's medical record within 24 hours following a dose of nimodipine. In an attempt to eliminate possible confounders, other medications and nutritional supplementation administered in the 24 hours preceding diarrhea occurrence were collected. These agents included docusate,

bisacodyl, senna, polyethylene glycol 3350, magnesium citrate, and magnesium hydroxide, antibiotics, or enteral nutrition. The lowest Systolic Blood Pressure (SBP) 24 hours before initiation of either nimodipine formulation was used as the patient's baseline measurement and the decrease in SBP in the first 24 hours following nimodipine initiation was recorded. The lowest SBP was recorded for each day the patient received treatment with nimodipine to evaluate the effect over time. The percentage of days on nimodipine therapy that each patient experienced at least one hypotensive event was recorded and compared between formulations. A hypotensive event was defined as SBP < 120 mmHg with severe hypotension defined as SBP < 100 mm Hg.

Descriptive statistics were used to summarize patient characteristics. Chi-Square, Wilcoxon Mann-Whitney, Wilcoxon-Rank, and Fisher's Exact tests were performed to compare adverse events between groups with an alpha level of less than 0.05 considered statistically significant. Statistical analysis was performed using JMP(R) Pro 11 software (SAS, Cary, NC).

Results

Of the 126 aSAH patients included in this study, 17 received NOS and 109 received NOC. Baseline characteristics between the two groups were comparable (Table 1). In total, 69 (54.7%) patients experienced diarrhea and received a dose of nimodipine in the 24 hours preceding the episode. As shown in Table 2, there was a statistically significant difference in the incidence of diarrhea between the two groups (NOS 82.4% and NOC 50.5%; p=0.02). There was no significant difference in the average time from initiation of nimodipine to the first incidence of diarrhea (NOS 8 days vs NOC 7.5 days; p=0.35). When comparing the impact of concomitant diarrhea-inducing medication therapies, there was no significant difference between groups. However, patients who received enteral nutrition did experience diarrhea more often than those who did not. Of the 69 patients who experienced diarrhea, 94% received a concomitant laxative agent (Table 3).

Variables	NOC (n=109)	NOS (n=17)
Mean age (SD), years	54 (15)	56 (9)
Sex, Male (%)	67 (61.5)	12 (70.6)
Race, n (%)		
Caucasian	44 (40.4)	5 (29.4)
African American	60 (55)	12 (70.6)
Other	5 (4.6)	0

Table 1: Patient Characteristics.

	NOC (n=109)	NOS (n=17)	p value
Diarrhea	55 (50)	14 (82.4)	0.02

Table 2: Diarrhea Incidence Within 24 Hours Following Nimodipine Administration.

	NOC (n=55)	NOS (n =14)	p value
Antibiotics	46 (83.6)	7 (50.0)	0.81
Enteral nutrition	14 (25.5)	5 (35.7)	< 0.01
Any bowel agent	51 (92.7)	14 (100)	0.36
One bowel agent	9 (16.4)	4 (28.6)	0.49
Two bowel agents	30 (54.5)	5 (35.7)	0.12
Three bowel agents	12 (21.8)	5 (35.7)	0.24

Table 3: Concomitant Therapies in Patients with Diarrhea.

Patients receiving NOS experienced a median SBP reduction of 22 mmHg after 24 hours of therapy compared to 35 mmHg receiving NOC (p=0.06) (Table 4). The average lowest SBP while on nimodipine therapy was 108 mmHg in the NOS group versus 106 mmHg in the NOC group (p=0.13). An analysis of the incidence of hypotension (days with SBP less than 120 mm Hg) and severe hypotension (less than 100 mm Hg) indicated no significant difference between groups. Patients experienced these adverse events 79% and 23% of the days on NOC therapy and 70% and 20% of days on NOS therapy, respectively. Doses were decreased from 60 mg to 30 mg in 24% of NOS patients versus 61% of NOC patients (p=0.18) in response to a significant decrease in SBP.

	NOC (n=109)	NOS (n =17)	p value
Patients with SBP Decrease[a]	101 (93.5)	14 (87.5)	0.39
Decrease in SBP[b,c]	35 mmHg (22,57)	22 mmHg (9,47)	0.06
Percent of days SBP was < 120 mm Hg[b]	79% (51,99)	70% (42,97)	0.38
Percent of days SBP was < 100 mm Hg[b]	23% (10,45)	20% (10,30)	0.56
Patients with Dose Decrease[a]	66 (60.6)	4 (23.5)	0.18
[a]Data reported as n (%); [b]Data reported as median (IQR); [c]24 hours after the first dose of therapy			

Table 4: Comparison of Systolic Blood Pressure Effects Between NOC and NOS.

Discussion

To our knowledge, this is the first study to evaluate the safety profile of nimodipine therapy in aSAH patients, specifically comparing oral capsule and oral solution formulations and the incidence of hypotension and diarrhea.

The results from this study show a statistically significant increase in the incidence of diarrhea in patients receiving NOS compared to NOC. Diarrhea can be a serious side effect of nimodipine leading to increased hospital length of stay, cost, and time to recovery [9]. All patients who received NOS were also receiving at least one diarrhea-inducing agent that could have contributed to diarrhea occurrence in these patients, but a similar proportion of patients on NOC were receiving these medications. Caution should be used when administering NOS as it contains polyethylene glycol and can exacerbate diarrhea when used in combination with other agents known to cause diarrhea, such as bowel regimens that include stool softeners and/or laxatives commonly used in intensive care units.

Our study also showed that over 90% of aSAH patients treated with either formulation of nimodipine experienced hypotension. Patients experienced hypotension (a SBP < 120 mm Hg at least 1 time per day) more than 70% of the days on therapy and severe hypotension (a SBP < 100 mm Hg at least 1 time per day) more than 20% of days on therapy. This is of great clinical concern and warrants further investigation as a severe drop in SBP can lead to cerebral ischemic events after aSAH. These results differ from the findings of Kieninger et al, which examined the incidence of arterial hypotension among patients receiving nimodipine as an oral tablet, oral solution, and continuous intra-arterial infusion. In this study of 1,835 oral doses of nimodipine administered, the rate of relevant drops in blood pressure, defined as SBP <100 mm Hg or requiring an increase in norepinephrine dose, was significantly higher after administration of NOS compared to NOC [10]. These differences may be attributed to the use of FDA approved products in our study versus other formulations being used in the study conducted outside of the United States, as well as the use of vasopressors as a marker of hypotension when this could have been used for induced hypertension for vasospasm.

Due to the increased reports of diarrhea with NOS in our aSAH patients, our institution switched back to using NOC. NOC appeared to be associated with a lower incidence of diarrhea in our patient population, has a longer history of use, and is cheaper based on the current Average Wholesale Price (AWP) than NOS. A cost analysis of the various formulations was performed based on VCUH acquisition cost and pharmacy technician pay (Table 5). The cost of a 21-day course of NOS was four times more expensive than NOC and NOC compounded oral syringes, even after accounting for the cost of medication, supplies, and pharmacy technician time.

NOC	
Oral capsule	$1,592.64
Oral syringe	$1,769.04#
NOS	$7,192.38
*Based on VCU wholesale acquisition cost of a 21-day course of nimodipine 60 mg every 4 hours #Plus supplies and technician time	

Table 5: Cost* Comparison of Nimodipine Formulations for a 21-day Course.

In June of 2018, a change in the NOS formulation was approved by the FDA. This updated formulation is bioequivalent to the previous oral solution, is available in a higher concentration of 60 mg per 10 mL, and has a 44% reduction in the amount of polyethylene glycol per dose. The average wholesale price for the newest formation of NOS is $10,299.24 for a 21-day course. The most common adverse effects of the new formulation are hypotension, headache, nausea, and bradycardia [10,11]. Additional studies are currently ongoing by the Pharmacy Section of the Neurocritical Care Society to evaluate this newest formation's safety profile.

Due to this study being retrospective in nature, there are some limitations that should be considered. A small sample size and the fact that a majority of the patients in our study were middle-aged African Americans may impact external validity. The NOS group was much smaller than the NOC group, therefore reducing power and increasing the possibility of type II error. There are several confounding factors that may have impacted the incidence of diarrhea besides the ones analyzed in this study (enteral nutrition, bowel regimen, and antibiotic usage). Hospitalized patients may be exposed to infectious causes of diarrhea (e.g., Clostridium difficile) or may have received other diarrhea-inducing therapies that were not accounted for in this study. Blood pressure was analyzed in this study, and these data may have been impacted by factors that were unable to be accounted for, including the stress of hospitalization, pain, medication adverse effects, and differing antihypertensive treatment regimens. The measures analyzed were obtained from patient chart reviews, which leaves room for error in data entry in the medical record or during transcription.

With many hospitals still using NOC in compounded syringes, this practice should be more closely evaluated to avoid patient harm and potential administration safety issues. Timely and consistent blood pressure readings should be monitored for all aSAH patients and patients on nimodipine should be carefully observed for drops in SBP, especially if they are experiencing vasospasm. The current standard of care at our institution is to reduce the dose and increase the frequency of administration of NOC for patients whose blood pressure decreases to harmful levels

post dose. Prospective studies evaluating the safety of nimodipine formulation administration with current concomitant management strategies should be conducted to determine if there is a safer alternative for aSAH patients.

Conclusion

This study compared the safety profile of NOC to NOS and found a statistically significant increase in the incidence of diarrhea when using NOS in patients with aSAH. In addition, both formulations produced a clinically significant reduction in systolic blood pressure which can lead to poor outcomes in this patient population. Large, prospective studies are needed to determine the overall safety of nimodipine formulations in aSAH patients to determine risk versus benefit associated with potential complications, such as diarrhea and SBP reductions, and determine the most cost-effective formulation to optimize patient care.

The authors confirm that authorship requirements have been met and the final manuscript was approved by all authors.

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