Nimodipine in Clinical Practice: A Pharmacological Update

Brendon Clough, Josephine Tenii, Claribel Wee, Elizabeth Gunter, Tara Griffin, Venkatesh Aiyagari

NCPD 2.0 ANCC Contact Hours 2.0 Rx credit

ABSTRACT

INTRODUCTION: Enteral nimodipine provides a neuroprotective effect in patients who have experienced an aneurysmal subarachnoid hemorrhage (aSAH). Nimodipine remains the only US Food and Drug Administration–approved medication for aSAH. **CONTENT:** Nimodipine has been prescribed for patients with aSAH; however, little is known about factors to consider regarding dosing or patient-specific variables that may affect tolerability to nimodipine. Clinical impact of dose or dosing frequency changes has also been much debated based on risk of hypotension with currently approved dosing regimens. **CONCLUSION:** This review article addresses factors to consider for dosing and administration, pharmacokinetic and pharmacogenetic impact on nimodipine, and, finally, drug interaction considerations to assess as patients are initiated on enteral nimodipine for aSAH.

Keywords: aneurysm, nimodipine, Nimotop, nursing, Nymalize, pharmacology, stroke, subarachnoid hemorrhage, cerebral artery vasospasm

Oral nimodipine, approved in the United States by the Food and Drug Administration in 1988, is a mainstay of therapy for patients after aneurysmal subarachnoid hemorrhage (aSAH). It has been shown to improve neurological outcomes and is recommended for all aSAH patients (class I, level of evidence A).[1] Nimodipine is a calcium channel blocker that inhibits calcium ion transfer into smooth muscle cells and inhibits vascular smooth muscle contractions. It was shown in animal experiments to have preferential effects on cerebral arteries due to its ability to cross the blood-brain barrier, a result of its high lipophilicity. However, the mechanism of benefit in aSAH patients remains largely unknown. It was originally thought to help reduce vasospasm in aSAH patients; however, arteriographic studies have shown inadequate effects on the relief of vasospasm in cerebral arteries.[2] The most well-known adverse effect of nimodipine is hypotension, which occasionally creates the need for dose reduction or even complete cessation of the medication. In a prospective study of 38 patients with subarachnoid hemorrhage, the intended full dose of nimodipine was administered on only 57.2% of the examined days.[3]

Dosing and Administration

Nimodipine should be started within the first 24 hours of admission in patients presenting with aSAH. [1] It is dosed at 60 mg every 4 hours for a total of 21 days post ictus. It is administered by mouth or through an enteral tube as either two 30-mg capsules (Nimotop) or 60 mg of an oral solution (Nymalize). Nymalize was recently reformulated from a concentration of 3 mg/mL to 6 mg/mL. This new formulation is available as 30 mg per 5 mL or 60 mg per 10 mL of prefilled oral syringe. After administration of the oral solution, the administration syringe should be refilled with 10 mL of 0.9% saline water solution and the remaining contents should be flushed into the enteral feeding device. If the patient is unable to swallow capsules and the oral solution is unavailable, the contents of the liquid-filled gel capsule may be manually extracted by creating a hole in both ends of the capsule with an 18-gauge needle and withdrawing the contents into an oral syringe.[2] The contents should be administered

Questions or comments about this article may be directed to Venkatesh Aiyagari, MD, at Venkatesh.Aiyagari@UTSouthwestern.edu. V.A. is a Professor at the Departments of Neurological Surgery and Neurology, and Chief of the Division of Neurocritical Care, University of Texas Southwestern Medical Center, Dallas, TX.

Brendon Clough, PharmD, is PGY2 Critical Care Pharmacy Resident, Texas Health Presbyterian Hospital, Dallas, TX.

Josephine Tenii, PharmD BCPS BCCCP, is Neurocritical Care Pharmacist Specialist, University of Texas Southwestern Medical Center, Dallas, TX.

Claribel Wee, MD, is Neurocritical Care Fellow, University of Texas Southwestern Medical Center, Dallas, TX.

Elizabeth Gunter, BSN RN CCRN SCRN, is Clinical Nurse Educator, Neuroscience, University of Texas Southwestern Medical Center, Dallas, TX.

Tara Griffin, BSN RN SCRN, is Clinical Nurse Educator, Neurocritical Care, University of Texas Southwestern Medical Center, Dallas, TX.

The authors declare no conflicts of interest.

https://doi.org/10.1097/JNN.0000000000000625

into the patient's enteral feeding device and flushed with 30 mL of 0.9% saline water solution afterward. Note that a US Boxed Warning exists with nimodipine for inadvertent intravenous administration of the liquid contents of the capsule. The solution, prepared in a syringe, has been reportedly administered intravenously by nursing staff unfamiliar with the medication, resulting in severe adverse events and even death.[4] All syringes containing nimodipine should carry the label "Not for IV use." The use of nimodipine in pregnant women is still unclear. Although animal studies have shown potential teratogenic effects, there have been no well-controlled studies in human patients.[2] The decision regarding nimodipine treatment in pregnant patients should be made based on a risk-benefit analysis for each patient.

Nimodipine dose reduction is sometimes initiated as a measure to meet the higher blood pressure goal. When hypotension occurs, the dose is often decreased to 30 mg every 2 hours or even discontinued altogether.[2,5] However, nimodipine dose reduction has been shown to result in subtherapeutic serum nimodipine levels.[6] Furthermore, recent retrospective trials have shown an association between decreased or discontinued nimodipine and worsened long-term functional outcomes.[7,8] Hypotension was found to be 3 times more common with the oral solution than the tablet (formulation not available in the United States) despite similar plasma concentration.[3] Hypertension is often induced, at times with the use of vasopressors, to increase cerebral perfusion in patients who go on to develop cerebral vasospasm.[9] In patients with refractory hypotension after nimodipine administration, vasoplegia should be suspected. Suggested management in patients who are refractory to fluid resuscitation and high-dose vasopressors (>0.5 mcg/kg per minute of norepinephrine) include methylene blue or hydroxycobalamin. However, more studies are needed to guide the appropriate treatment regimen.[10]

Pharmacokinetics

The pharmacokinetics of nimodipine are important to consider to maximize the benefits while minimizing adverse effects. Upon oral administration, rapid absorption takes place, resulting in peak concentrations within only 1 hour. The short half-life (1–2 hours) creates the need for frequent dosing. Nimodipine is highly protein-bound (>95%) and has a bioavailability of only 13%, because of its high first-pass metabolism. Its elimination is nearly entirely through formation of minimally active metabolites, with less than 1% excreted unchanged in the urine. A specific liver enzyme (CYP3A4) plays the largest role in nimodipine metabolism and is responsible for many of its drug-drug interactions.[2,5]

Numerous patient factors have been found that may potentially require dosing adjustments. Because of nimodipine's high first-pass metabolism in the liver, dose reduction may be necessary in patients with hepatic cirrhosis, as the maximum concentration (Cmax) has been shown to increase 2-fold in this population. Studies are needed to assess what dose and frequency reduction will result in sustained neurological benefit. An increase in the area under the plot of plasma drug concentration versus time after the drug is administered (also known as "area under the curve") and Cmax of nimodipine have also been seen in elderly patients, although this is thought to be clinically insignificant.[2] Furthermore, a study performed on 24 healthy male volunteers showed important pharmacokinetic effects caused by food consumption. After a standard breakfast, a 68% decrease in Cmax was observed, as well as a 38% reduction in bioavailability compared with fasting conditions.[2] Unfortunately, no information was provided regarding the content of the meals to rule out potential effects of protein binding resulting in decreased nimodipine concentration. Nonetheless, US labeling recommends that nimodipine be administered on an empty stomach at least 1 hour before or 2 hours after meals.[2,5] Adherence to this labeling can be impractical and may result in underfeeding, particularly for critically ill patients receiving continuous tube feedings given the frequent dosing requirement of nimodipine.

There is very little published data examining the interaction between nimodipine and different food products. Other factors that may equally affect nimodipine serum concentration such as specific drug-food binding, the effects of gastrointestinal motility, and changes in absorption along the gastrointestinal tract are also yet to be studied. However, grapefruit juice is a strong CYP3A4 inhibitor that has been shown to increase nimodipine bioavailability by 51% and Cmax by 24%.[10] From this information, it is possible to extrapolate likely food interactions from other studies that assess different foods known to alter CYP3A4 activity. A study[11] from 2015 investigated the interaction between CYP3A4 and dietary polyphenols. Polyphenols are found in many commonly consumed foods such as fruits, vegetables, coffee, tea, chocolate, alcohol, and various herbs. These foods were found to have varying effects on CYP3A4 activity. Whereas some increased the activity of CYP3A4, others did just the opposite; thus, patients should be clinically monitored because of variable effects of food on the CYP3A4 enzyme. Patients on parenteral nutrition should be closely monitored for hepatotoxicity resulting in changes to the metabolism of medications that rely on the liver.[12]

Because of hepatic metabolism via the CYP3A4 enzyme, drug-drug interactions with nimodipine are common.[13] This can be clinically important, because

CYP3A4 is recognized as the main enzyme responsible for the metabolism of drugs in the liver and gut.[11] A complete evaluation of the patient's current list of medications at the initiation of therapy is important. Although numerous drug-drug interactions exist with nimodipine, some of the more important interactions are summarized in Table 1. Of note, nimodipine may decrease the effect of clopidogrel and increase the effect of antipsychotic agents, duloxetine, levodopa, magnesium, and nondepolarizing neuromuscular blockers.[4]

Pharmacogenomics

Pharmacogenomics seem to play a role in the pharmacokinetics and pharmacodynamics of nimodipine.[14] A recent study from China investigated the effects of polymorphisms in CYP3A5, MDR1, and CACNA1C and found that CYP3A5*1, CYP3A5*3, and CACNA1C genes have effects on both disposition and response in healthy male volunteers.[15] Subjects with homozygous CYP3A5 *3/*3 were shown to have decreased clearance of nimodipine compared with those with heterozygous *1/*3 or wild-type *1/*1 genes. Single-nucleotide polymorphisms of the CACNA1C gene played a role in nimodipine efficacy as well. Some of these single-nucleotide polymorphisms were even found to increase rates of hypotension. However, these results have not yet been replicated in other studies and are therefore currently only categorized as level 3 evidence as per PharmGKB.[16]

Conclusion

Various food products and medications interact with nimodipine. Patient characteristics such as age, renal function, and hepatic function also play a role in nimodipine dosing. Higher nimodipine concentrations can increase the risk of adverse effects, namely, hypotension. Decreased nimodipine concentrations may worsen neurological outcomes in a disease with high morbidity and mortality. Studies assessing interactions with specific foods and enteral or parenteral formulations are almost nonexistent with nimodipine. Some data may be extrapolated from studies investigating CYP enzyme interactions with various products. However, there are numerous other factors that play a role in these effects. In addition, the frequent dosing of nimodipine makes interactions with food difficult to avoid. Interactions with specific medications, however, are more widely studied. These interactions stem mainly from effects on the liver, more specifically on the CYP enzyme system, as nimodipine is metabolized via CYP3A4. Strategic timing of medications and the use of alternative options when feasible may help mitigate some of these interactions. Table 2 presents a summary of best practices with the use of nimodipine. Overall, it is important that providers understand the multitude of factors that play a role in the effects of nimodipine on patients presenting with aSAH. Further data assessing how food products, age, hepatic impairment, and other factors will be helpful to guide dosage adjustments and improve patient care.

TABLE 1. Significant Nimodipine Drug-Drug Interactions

Increase Nimodipine Concentration	Decrease Nimodipine Concentration
Valproic acid	Carbamazepine (8–10 times lower)
Azole antifungal agents	Phenobarbital (8–10 times lower)
Fluoxetine	Phenytoin (8–10 times lower)
Macrolides	Calcium salts
Magnesium salts	St John's wort
HIV and HCV protease inhibitors	
Conivaptan	

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency syndrome.

TABLE 2. Short Summary of Nimodipine Use Best Practices

Do…	Do Not…
Give full-dose nimodipine when patient tolerates	Give nimodipine intravenously
Time administration apart from food when feasible	Give patient grapefruit juice
Assess other medications for drug-drug interactions	

Acknowledgments

The authors thank the Neuroscience Nursing Research Center for assistance with manuscript development.

References

1. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. *Stroke*. 2012;43:1711–1737. doi:10.1161/STR.0b013e3182587839
2. Nimotop [Package insert]. Bayer Pharmaceuticals Corporation; 2005. https://resources.bayer.com.au/resources/uploads/PI/file9406.pdf. Accessed October 25, 2021.
3. Kieninger M, Gruber M, Knott I, et al. Incidence of arterial hypotension in patients receiving peroral or continuous intra-arterial Nimodipine after aneurysmal or perimesencephalic subarachnoid hemorrhage. *Neurocrit Care*. 2019;31(1):32–39. doi:10.1007/s12028-019-00676-w
4. FDA Drug Safety Communication: serious medication errors from intravenous administration of nimodipine oral capsules. Food and Drug Administration Web site. Updated August 3, 2017. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-serious-medication-errors-intravenous-administration-nimodipine-oral. Accessed October 16, 2020.

5. Nimodipine. In: *Lexi-Drugs [database online]*. Hudson, OH: Wolters Kluwer Health. Accessed October 2, 2020.
6. Turnbull MT, Ross O, Lesser E, et al. Pharmacogenomics of nimodipine in aneurysmal subarachnoid hemorrhage. Poster presented at: Neurocritical Care Society Annual Meeting; September 22-25, 2020.
7. Sandow N, Diesing D, Sarrafzadeh A, Vajkoczy P, Wolf S. Nimodipine dose reductions in the treatment of patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2015;25(1):29–39. doi:10.1007/s12028-015-0230-x
8. Hernandez-Duran S, Mielke D, Rohde V, Malinova V. Does nimodipine interruption due to high catecholamine doses lead to a greater incidence of delayed cerebral ischemia in the setting of aneurysmal subarachnoid hemorrhage? *World Neurosurg*. 2019;132:e834–e840. doi:10.1016/j.wneu.2019.08.001
9. Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Crit Care*. 2016;20(1):277. doi:10.1186/s13054-016-1447-6
10. Clifford KM, Madhok J, Murray NM, Mohindra V. Rescue of nimodipine-induced refractory vasoplegia with hydroxocobalamin in subarachnoid hemorrhage: a case report. *Crit Care Explor*. 2020;2(10):e0205. doi:10.1097/CCE.0000000000000205
11. Basheer L, Kerem Z. Interactions between CYP3A4 and dietary polyphenols. *Oxid Med Cell Longev*. 2015;2015:854015. doi:10.1155/2015/854015
12. Ekincioglu AB, Demirkan K. Clinical nutrition and drug interactions. *Ulus Cerrahi Derg*. 2013;29(4):177–186. doi:10.5152/UCD.2013.112013
13. Muck W, Ahr G, Kuhlmann J. Nimodipine. Potential for drug-drug interactions in the elderly. *Drugs Aging*. 1995;6(3):229–242. doi:10.2165/00002512-199506030-00006
14. Peacock SH, James C, Turnbull MT, Cowart JB, Reid JM, Freeman WD. Pharmacogenomics of cytochrome P450 of nimodipine metabolism after aneurysmal subarachnoid hemorrhage. *J Neurosci Nurs*. 2019;51(5):238–242. doi:10.1097/JNN.0000000000000464
15. Zhao Y, Zhai D, He H, Li T, Chen X, Ji H. Effects of CYP3A5, MDR1, and CACNA1C polymorphisms on the oral disposition and response of nimodipine in a Chinese cohort. *Eur J Clin Pharmacol*. 2009;65:579–584. doi:10.1007/s00228-009-0619-6
16. Nimodipine. PharmGKB Web site. Available at: https://www.pharmgkb.org/chemical/PA450633/clinicalAnnotation. Accessed January 4, 2021.