Pharmacogenomics of Cytochrome P450 of Nimodipine Metabolism After Aneurysmal Subarachnoid Hemorrhage

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ABSTRACT

INTRODUCTION: Aneurysmal subarachnoid hemorrhage (aSAH) is a type of stroke that is life threatening with high rates of mortality, and many survivors are left with permanent neurologic deficits. Nimodipine is the treatment of choice for aSAH with the goal of reduction of delayed cerebral ischemia. It is the only evidence-based medication that has been shown to have improved outcomes for delayed cerebral ischemia; therefore, it is important for neuroscience nurses to be knowledgeable of the pharmacology and pharmacogenomics properties of this medication, including cytochrome P450 (CYP450) enzymes. **METHODS AND RESULTS:** This article reviews the CYP450 enzyme system including a review of the pharmacotherapy and pharmacogenomics of nimodipine for patients with aSAH illustrated with case study of a patient with abnormal drug metabolism. **CONCLUSION:** CYP450 enzymes can be inhibited or induced by multiple medications resulting in clinically significant differences in drug metabolism. Food and Drug Administration–approved medication nimodipine is the only medication shown to improve outcomes in patients with aSAH. Hence, it is important to have awareness of potential drug-to-drug interactions and pharmacogenomics of nimodipine when caring for critically ill patients with aSAH.

Keywords: CYP450, delayed cerebral ischemia, nimodipine, pharmacogenomics, pharmacotherapy, subarachnoid hemorrhage, precision medicine

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Case Study

A 44-year-old African American man with no medical history other than tobacco use presented to the emergency department with a chief complaint of "worst headache of his life." He was found to have modified Fisher grade 4, Hunt and Hess grade 3, and World Federation of Neurological Surgeons (WFNS) grade 2 subarachnoid hemorrhage (SAH) with a 2-mm–wide aneurysm at the left carotid terminus with mild hydrocephalus. He had an external ventricular drain placement with evidence of aneurysm rebleeding upon insertion. Cerebral angiogram was performed with coiling and stent placement of a ruptured left carotid terminus aneurysm. Intracranial stent placement was required to hold coils in place within the aneurysm. The patient was consented and enrolled in a research trial to look at the pharmacogenomics (PGX) of nimodipine, and serum CYP genotype testing was performed. He was then placed on nimodipine 60 mg every 4 hours as part of the standard of care for SAH. He had evidence of mild-to-moderate

cerebral vasospasm in his right middle cerebral artery on transcranial Doppler monitoring on hospital day 7 that persisted through hospital day 16. On hospital day 9, the provider team was notified that he had changes in his behavior and personality without any motor deficits. He was found to have right parietal cortical ischemia. See Figure 1 for images of computed tomography angiography on admission compared with images on day 9. Additional hospital course complications included cerebral salt wasting, headaches, and hypertension. He was able to be successfully weaned from his external ventricular drain on hospital day 15 and was able to be discharged to home on hospital day 17 without any neurologic deficits.

Background

Aneurysmal SAH (aSAH) makes up approximately 8% of all types of strokes.[1] However, aSAH carries a higher mortality compared with the more common ischemic strokes. The 1-month mortality rate of aSAH is as high as 45%, and one-third of survivors are left with permanent neurologic deficits.[1] Approximately 3% of the population has asymptomatic intracranial aneurysms that have the potential to rupture and cause an acute aSAH.[1] Although the incidence of aSAH has not changed for the past 30 years, aSAH mortality rates have fallen with the development of specialized multidisciplinary neuroscience intensive care units, quick repair of aneurysms, discovery of antifibrinolytic treatment to prevent aneurysm rebleeding, and discovery of the neuroprotective benefits of the use of nimodipine.[2]

The typical aSAH presentation is that of a "thunderclap" headache or a sudden-onset, excruciating headache that is often described as "the worst headache of one's life." It can be accompanied by subsequent meningismus or neck pain, photophobia, nausea, vomiting, and loss of consciousness. Associated conditions with aSAH include autosomal dominant polycystic kidney disease, Ehlers-Danlos syndrome type IV, cerebral arterial venous malformations, fibromuscular dysplasia, and Marfan syndrome. Modifiable risk factors are hypertension and substance abuse (eg, tobacco, alcohol, cocaine). Nonmodifiable risk factors include personal or family history of aSAH, older age, female sex, and African American, Hispanic, Japanese, or Finnish ethnicity.[3]

The diagnosis of aSAH is obtained by noncontrast head computed tomography (CT) scan, which has 99% to 100% sensitivity and specificity when performed within 6 hours of symptom onset.[3] Computed tomography angiography is useful to evaluate location and morphologic features of the aneurysm. Digital subtraction angiography is the criterion standard of imaging of cerebral vasculature. Aneurysmal SAH is classified by disease scoring severity using the Hunt and Hess grading scale, the WFNS, and the modified Fisher grading scale. The Hunt and Hess scale and WFNS are used to characterize patients on their clinical presentation, and the modified Fisher scale is used to estimate symptomatic vasospasm risk.[4]

FIGURE 1   Cerebral Angiogram Images: Hospital Admission (Right) and Hospital Day 9 (Left). Arrows Highlight Right Middle Cerebral Artery M1 Branch Vasospasm and Stent Coiling of Aneurysm
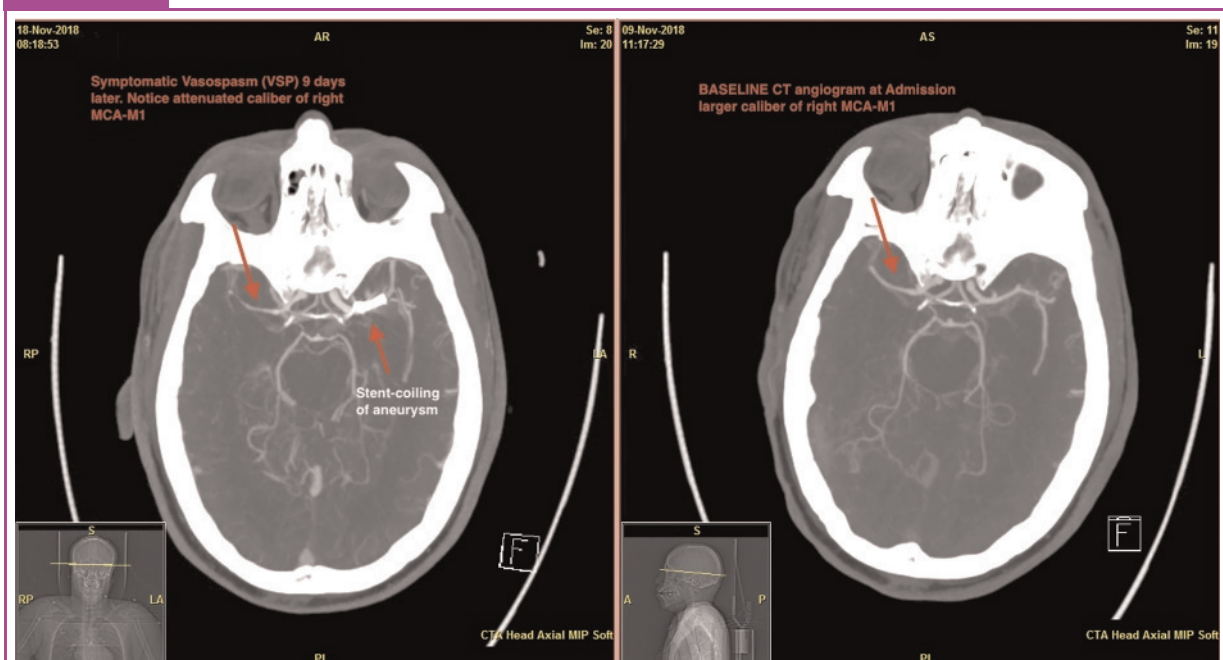
Nimodipine for Prevention of Delayed Cerebral Ischemia in aSAH Patients

Pharmacotherapy has an established well-validated role within several aspects of aSAH and several emerging areas of research in other aspects. Current pharmacologic approaches that have been evaluated in the treatment of aSAH include treatment to reduce the harmful effects of subarachnoid blood and prevent aneurysm rebleeding, and treatment to reduce the risk of delayed cerebral ischemia (DCI) or vasospasm.[1] The main focus of pharmacologic treatment of aSAH is the prevention of DCI. DCI is most commonly caused by cerebral vasospasm but can also be caused by microthrombosis, cortical spreading depolarizations, or other related ischemia.[5] The only Food and Drug Administration (FDA)–approved pharmacologic therapy with neuroprotective effects and improvement of outcomes for aSAH is the use of nimodipine.[1]

Nimodipine is a calcium channel antagonist of the dihydropyridine family that works primarily on vascular and cardiac smooth muscle fibers preventing vasoconstriction.[6] It differs from other dihydropyridine calcium channel blockers because of its ability to cross the blood-brain barrier and dilate cerebral arteries. In randomized controlled trials, patients on FDA-approved nimodipine pharmacotherapy have been shown to have fewer incidences of cerebral infarction and better functional outcomes at 3 months compared with placebo.[6] Furthermore, nimodipine reduced the incidence of poor neurologic outcomes by 40%, which is defined as death, persistent vegetative state, and severe disability. There have not been data that nimodipine decreases the frequency of angiographic vasospasm.[2]

After oral administration, nimodipine is rapidly and almost completely absorbed and, generally, maximal concentrations are achieved within 1 hour. The FDA-approved standard oral dose of nimodipine for patients with aSAH is 60 mg every 4 hours for 21 days after aSAH.[7] The most common adverse effect with the administration of nimodipine is systemic hypotension. If this occurs, the dose can be changed to 30 mg every 2 hours or 15 mg every hour. It has been shown that a significant percentage of patients with aSAH receiving nimodipine develop systemic arterial hypotension after taking the drug at the FDA controlled dose.[8] Systemic hypotension can potentially cause a reduction in cerebral blood flow and cerebral perfusion pressure particularly in patients with vasospasm. Despite being almost completely absorbed after enteral ingestion, the bioavailability of nimodipine is only 5% to 10% in young patients and 10% to 15% in older patients because of it undergoes an extensive first-pass hepatic metabolism that is performed predominantly by cytochrome P450 (CYP450) subtypes CYP3A4 and CYP3A5.[7]

Given that nimodipine is the only evidence-based medication for DCI, it is important for neuroscience nurses to be aware of the various types of medications that may be given concurrently in patients with SAH to be knowledgeable about the potential pharmaceutical, pharmacokinetic, and pharmacodynamic interactions. Interactions can include abnormalities with absorption, distribution, metabolism, or excretion.[9] The most important class of pharmacologic interactions involves the CYP450 microsomal enzyme system, which is the major enzyme system for phase I metabolism of medications including nimodipine.[9,10] There are multiple human isoforms of CYP450, and these isoforms are given letters and numbers to signify their families, subfamilies, and individual isoforms. The most clinically relevant cytochromes are CYP3A4, CYP3A5, and CYP2C19, with CYP3A4 being the most abundant enzyme.[11] CYP3A4 is particularly relevant to nimodipine metabolism because it is the predominant CYP metabolizer of the drug into inactive metabolites and because CYP3A4 has various inhibitors and inducers, which can affect nimodipine drug levels.[9] For example, grapefruit juice (a potent inhibitor of CYP3A4) when co-administered with nimodipine can increase the bioavailability 51% and peak concentrations. Furthermore, nimodipine drug levels dropped 7-fold in the presence of enzyme-inducing antiseizure medications such as phenytoin but increased 50% with valproate, which are common drugs in this population due to the comorbid presence of seizures or status epilepticus.[7] CYP2C19 inhibitors include commonly used medications pantoprazole and clopidogrel in this population, which would raise nimodipine levels.

CYP450 in Pharmacotherapy for SAH Treatment

Cytochrome P450 enzymes are iron-containing enzymes that have a wide variety of functions. They are essential for the detoxification of foreign chemicals, metabolism of many different drugs, and productions of steroids, cholesterol, and hormones.[12] The CYP450 class has 6 enzymes responsible for the metabolism of 90% of pharmacotherapies. A CYP450 enzyme can be either induced or inhibited by drugs that can result in clinically relevant drug-to-drug interactions. It is important for providers to be aware of drugs that are metabolized by the CYP system and which ones are the most potent inducers or inhibitors to minimize the possibility of adverse medication reactions.[12]

There are multiple different factors for individual differences in drug responses including drug-to-drug interactions, environmental factors, and clinical factors that can influence patient outcomes. Differences in individual drug responses have led to complexity in understanding individual differences.[10] There are 3 main concepts involved with CYP450-mediated drug metabolism that include CYP inducers, inhibitors, and substrates.

CYP inducers are substances that ultimately decrease concomitant drug levels by increasing activity of CYP450 enzymes, which may accelerate conversion to inactive metabolites.[9] CYP inhibitors typically increase concomitant drug levels via mutual competition or enzyme inactivation of substrates for a catalytic site. CYP inhibitors may prolong drug half-life by affecting substrates and/or increase pharmacodynamic drug peak levels by decreasing the rate of drug metabolism.

It is important to consider different types of medication that are commonly used in caring for patients with aSAH and how those medications could possibly inhibit or induce nimodipine levels. Studies have shown that polymorphisms in the CYP3A4 and CYP3A5 genotypes can potentially affect serum concentrations of nimodipine; thus, this is an important area of upcoming research.[2] Given that nimodipine is the only medication that is FDA approved with positive evidence for improved outcomes, there is not an alternate medication that can be given. The most common enzyme types that affect nimodipine metabolism are CYP3A4, CYP3A5 and CYP2C19.[7]

It is important to understand potential drug-drug interactions between CYP inhibitors, substrates, and inducers. There are multiple different CYP enzymes including CYP3A4, CYP3A5, CYP2D6, and CYP2C19, as well as substrates, inhibitors, and inducers commonly used in the neuroscience intensive care unit that can affect nimodipine metabolism. CYP3A4 inducers include phenytoin and modafinil, which could lead to reduced levels of nimodipine. CYP2C19 substrates include midazolam with dexmedetomidine as an inhibitor, which could lead to increased levels of nimodipine.[7] CYP2C19 inducers include phenytoin and barbiturates, whereas inhibitors include clopidogrel, pantoprazole, fluoxetine, and modafinil. CYP3A5 substrates include fentanyl, midazolam, and simvastatin, and grapefruit juice is an inhibitor.[7] Dexamethasone can be either an inducer or inhibitor, which can lead to either an increase or decrease in nimodipine levels; thus, caution should be used with using this medication with nimodipine because of the unknown effect on metabolism. The patient in the case study was on multiple different substrates, inhibitors, and inducers that, when given with nimodipine, can cause an increase or decrease in serum levels. He was given midazolam for sedation during the cerebral angiogram and dexamethasone for headache management and was required to be on clopidogrel because of the fact that he required an intracranial stent.

Molecular Pharmacology and Experimental Therapeutics and Genomics

In addition to being aware of the pharmacologic reactions that can occur with nimodipine with other pharmacologic treatments, it is also important to think about the genetic factors that can affect nimodipine drug metabolism. Pharmacogenomic testing is the study of genetic differences on a patient's response to a certain medication and can assist with optimizing drug dose-response relationships, and minimize adverse drug reactions, and side effects in patients.[10] The ability to metabolize a drug along a specific pathway of the CYP450 enzyme system can be modulated by genetic polymorphisms, and PGX testing can be performed to determine enzyme activity and investigate the differences in PGX type to classify patients as a poor, intermediate, normal, or ultra-rapid metabolizer.

The predominant nimodipine metabolism CYP450 enzyme isoforms are CYP3A4, CYP3A5, and CYP2C19, of which there are multiple allele variants for each CYP subtype. The combinations of the alleles for each CYP subtype make the metabolizer type and are typically classified as "extensive," "average," "intermediate," and "poor" metabolizer. Extensive metabolizers of nimodipine will have the ability to tolerate the standard dose of 60 mg every 4 hours with minimal adverse effects such as hypotension compared with poor or immediate metabolizer genotypes. Intermediate metabolizers metabolize the drug normally and tolerate the drug well. The patient in our case study was found to have had genotypes that classify him as an intermediate to extensive drug metabolizer at CYP3A4 and CYP3A5.

Summary and Future Practice Considerations

To date, there is a lack of PGX studies evaluating patient differences of metabolism of nimodipine in aSAH patients, specifically to individualize the dosing according to patient PGX type. The original randomized trials studying nimodipine occurred before the advent of precision medicine and PGX testing, and thus future trials are needed to investigate PGX type and patient outcomes. Delayed cerebral infarction or DCI is the leading cause of morbidity of patients who survive the initial SAH, and it occurs in 33% of patients, despite 100% of patients receiving nimodipine.[13] Risk factors for DCI include modified Fisher grade 3 or 4 bleeding, poor clinical neurologic examination, substance abuse including cocaine and tobacco, nonconvulsive seizures, hydrocephalus, and loss of consciousness at presentation.[13] The impact of these risk factors relative to nimodipine PGX testing or genotype remains to be studied. Delayed cerebral ischemia is a diagnosis of exclusion and is defined when all other causes of neurologic deterioration have been excluded (eg, procedure-related stroke or medical causes). Vasospasm, which is vascular narrowing seen on neuroimaging such as CT angiogram or cerebral angiogram, occurs in up to 70% of aSAH patients but is not always associated with clinical or symptomatic DCI.[14]

The patient in our case study presented with a modified Fisher grade 4 SAH with a history of tobacco use, which increased the odds for vasospasm and DCI. This patient case underwent PGX testing, was found to be a rapid or extensive metabolizer of nimodipine, and subsequently developed angiographic evidence of cerebral vasospasm on his CT angiogram; however, he had minimal clinical symptoms or manifestations. Considering the devastating effects that DCI can have on mortality and functional outcomes in patients with aSAH, it is important to be aware of the pharmacologic and PGX factors that may affect drug metabolism. Neuroscience nurses should be aware of the different types of pharmacologic interactions that patients are prone too, particularly in critically ill patients such as those with aSAH. Future research should be geared toward individualized medicine and include genetic testing on patients with aSAH. The results of the testing would determine the "right dose for the right patient" of nimodipine for a given patient PGX profile.

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