Variation in Nimodipine Exposure and its Effect on Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage

by

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Abstract

Aneurysmal Subarachnoid Hemorrhage (SAH) is a life-threatening neurological emergency caused by a ruptured brain aneurysm leading to extravasation of blood into the subarachnoid space. SAH accounts for 5-10% of all strokes, affecting relatively younger age compared to ischemic strokes, leading to premature loss of productive life years. Neurological and medical complications are common following SAH and contribute significantly to patient outcomes. Delayed cerebral ischemia (DCI) and vasospasm are the main challenges that contribute to post SAH unfavorable patient outcomes. The Only Health Canada and FDA approved drug to prevent these two complications is nimodipine, a calcium channel blocker. Guidelines recommend that all patients with SAH to receive a fixed dose of oral nimodipine for 21 days. However, review of literature pertaining to nimodipine pharmacokinetics demonstrated extensive pharmacokinetic variability among different group of patients. Furthermore, limited evidence suggested lower exposure of the drug following enteral feeding administration compared to oral dosing. It is not clear if all patients are getting the full benefit of nimodipine. Therefore, our research aimed first to investigate retrospectively the impact of administering nimodipine via enteral feeding tubes on outcomes in patients with SAH. Second, we aimed to develop and validate an enantioselective assay for nimodipine to be utilized in our pilot study. Third, we aimed to conduct a prospective pilot study aimed to preliminarily determine potential factors that might have an influence on nimodipine exposure and to investigate whether there is a trend of possible association between nimodipine exposure and patient outcomes (vasospasm, DCI, and modified Rankin Scale (mRS) at 90 days post SAH admission). For the first objective, a retrospective chart review study was carried out that involved reviewing 85 charts for patients admitted to the University of Alberta Hospital. Following adjustment for disease severity, nimodipine administration through feeding tubes was

associated with vasospasm in the first 7 days of patient admission where patients receiving nimodipine via enteral feeding tubes had increased odds of vasospasm compared to those administered it as whole tablets (OR 8.9, 95% CI 1.1-73.1, *p* value 0.042). When analyzed over the 21-day period, nimodipine administration by feeding tube was associated with increased odds of DCI compared to whole tablets (OR 38.1, 95% CI 1.4-1067.9, *p* value 0.032). For the enantioselective assay development, we presented an LC-MS/MS method for quantifying nimodipine enantiomers in human plasma using a small sample volume (0.3 ml) and a single liquid-liquid extraction step. The peak area ratios were linear over the tested concentration ranges (1.5-75 ng/ml) with $r^2 > 0.99$. The intraday and interday CV and percent error were within ±14% while that of the interday was within ±13% making this analytical method feasible for research purposes and pharmacokinetic studies. For our third objective, we were able to recruit 7 patients admitted to the University of Alberta Hospital. Blood samples were collected following a single nimodipine 60 mg dose at steady state. Plasma nimodipine enantiomers concentrations were quantified using the LC-MS/MS method that we validated. Area under the concentration-time curve ($AUC_{0\text{-}4h}$) was calculated. Factors that could influence plasma nimodipine concentrations were assessed in different patient categories. Both discharge outcomes and 3-months mRS were collected. Patients who took nimodipine through feeding tubes and those with high grade disease had a trend for lower systemic exposure. On the other hand, older patients had higher nimodipine exposure compared to younger ones. With regards to outcomes, the median $AUC_{0\text{-}4h}$ values for both nimodipine enantiomers were lower in the 2 patients who had developed vasospasm. There was also a trend for a lower (+)-R nimodipine exposure for patients who had modified Rankin Scale of 3 (worse outcome) than those who had an mRS of 1 (better outcome). In conclusion, the retrospective chart review findings suggested that nimodipine administration via enteral feeding

tubes may be associated with vasospasm and DCI in subarachnoid hemorrhage patients possibly secondary to reduced exposure. In addition, we hope the findings of our retrospective and the pilot studies to lay the foundation of a larger prospective observational study to investigate the association between nimodipine exposure and patient outcomes, a step towards nimodipine individualization in SAH patients.

Preface

This thesis is an original work by Fadumo Ahmed Isse. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "The Impact of Nimodipine Administration through Feeding Tube on Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage", Pro00089529, Project Name "Nimodipine Exposure and Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage: A Prospective Pilot Study", Pro00085618.

This thesis contains **three** published journal articles:

Part 2 (**1.1.2 nimodipine**) content of **chapter 1** with the exception of the RCT section has been published. I (Fadumo Ahmed Isse) am co-author in this paper where I contributed to around 35-40 % of the reviewing, writing and citing the articles, and creating the final draft.

Bibliography: Mahmoud SH, Ji X, Isse FA. Nimodipine Pharmacokinetic Variability in Various Patient Populations. Drugs in R&D. 2020. **Doi** : https://doi.org/10.1007/s40268-020-00322-3

Chapter 2 is a published journal article. I (Fadumo Ahmed Isse) contributed to study conception, design, data analysis, writing the first draft of the manuscript, revision, and approval of the manuscript.

Bibliography: Isse FA, Abdallah YEH, Mahmoud SH. The Impact of Nimodipine Administration through Feeding Tube on Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage. J Pharm Pharm Sci. 2020;23(1):100-8. **Doi** : https://doi.org/10.18433/jpps30960

Chapter 3 is a published journal article. I (Fadumo Ahmed Isse) contributed to performing all experiments, method validation, data analysis, writing the first draft of the manuscript, and revision of the manuscript.

Bibliography: Isse FA, Le T, Mahmoud SH. Enantioselective assay of nimodipine in human plasma using liquid chromatography-tandem mass spectrometry. Biomed Chromatogr. 2020:e4971. **Doi**: https://doi.org/10.1002/bmc.4971

This work is dedicated to

I am dedicating this work to my loved father (**Ahmed Isse Samatar**) who died in 2015 (may his beautiful soul rest in peace). This is just a very tiny achievement that I wanted to make him proud of me. I will be forever committed to honor his soul and keeping his legacy alive and my loving mother (**Barlin Kulmiye Cilmi**) who was with my side and helped me to get through the most difficult times; without her, I could not do many achievements including this big one, her prayers, love, and care helped me to accomplish this work.

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Table of Contents

List of tables

List of Figures

List of abbreviation and symbols:

AAG	Alpha-acid glycoprotein
ACOMM	Anterior communicating artery
AED	Antiepileptic drugs
AHA	American Heart Association
APACHE II	Acute Physiology and Chronic Health Evaluation II
aSAH	Aneurysmal Subarachnoid Hemorrhage
AUC	Area under the concentration-time curve
AUC_{0-4h}	Area under plasma drug concentration-time -curve from 0 time to 4 hours post dose
BBB	Blood brain barrier
BMI	Body mass index
CABG	Coronary artery bypass graft
CE	Collision energy
cGMP	Guanosine monophosphate
CKD	Chronic kidney disease
CL	Clearance
C_{max}	Maximum (or peak) serum concentration
C_{maxPO}	Peak plasma concentrations following oral administration
CSF	Cerebrospinal fluid
C_{ssivi}	Steady plasma concentrations following intravenous infusion
CSW	Cerebral salt wasting syndrome
CT	Computed tomography
CTA	CT angiography
CV	Coefficient of variation
CV	Coefficient of variation
CYP	Cytochrome P450
DAG	Diacylglycerol
DCI	Delayed Cerebral Ischemia
DID	Delayed ischemic deficit
DIND	Delayed ischemic neurological deficit
DSA	Digital subtraction angiography
DVT	Deep venous thrombosis
ESI+	Positive mode electrospray ionization source
ET-1	Endothelin-1
EVD	External ventricular drainage
FT21	Took the drug by feeding tube over 21 days period
FT7	Patients who took nimodipine by feeding tube (crushed) in the first week
GCS	Glasgow Coma Score
GOS	Glasgow Outcome Scale
HIU	High intensity unit
HQC	High level quality control
ICH	Intracerebral hemorrhage
ICU	Intensive care unit
IP3	Inositol-1, 4,5-trisphosphate
IS	Internal standard
IS	Internal standard
IV	Intravenous

IVH	Interventricular hemorrhage
Kg	Kilogram
L	Litre
LC- MS/MS	Liquid chromatography, tandem mass spectrometry
LC- MS/MS	Liquid chromatography, tandem mass spectrometry
LLOQ	Lowest limit of quantification
LP	Lumbar puncture
LQC	Low level quality control
MF	Matrix factor
mg	Milligram
min	Minutes
mL	Millilitre
MLC	Myosin light chain
MMP9	Matrix metalloproteinase 9
MQC	Middle level quality control
MRI	Magnetic resonance imaging
MRM	Multiple reaction monitoring
mRS	Modified Rankin Scale
NG	Nasogastric tube
NO	Nitric oxide
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
PCOM	Posterior communicating artery
PI3K	Phosphoinositide3-kinase
PK	Pharmacokinetics
PKC	Protein kinase C
PO7	Patients who took nimodipine by oral (as tablet) in the first week
QC	Quality control
RCTs	Randomized controlled trials
REDCap	Research electronic data capture
Rho	Ras homologous
ROC	Area under the receiver operating characteristic
ROS	Reactive oxygen species
SD	Standard deviation
SIADH	Syndrome of inappropriate antidiuretic hormone
SMCs	Smooth muscle cells
t ½	Half-life
TCD	Transcranial Doppler ultrasonography
T_{max}	Time at which C_{max} is attained
TNF-α	Tumor necrosis- α
t-PA	Tissue plasminogen activator
Vd	Volume of distribution
WFNS	World Federation of Neurological Surgeons Scale
µg	Microgram
µL	Microliter

Chapter 1 Introduction

Part 2 contents (**1.1.2 nimodipine**) of this chapter has been published; except the RCTs section

Sherif Hanafy Mahmoud[1], PhD; **Xinqi Ji,** Pharm D[1]**; Fadumo Ahmed Isse**[1], Pharm D. Nimodipine Pharmacokinetic Variability in Various Patient Populations. Drugs in R&D. 2020.

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1.1 Background

1.1.1 Aneurysmal Subarachnoid hemorrhage

1.1.1.1 Overview

Aneurysmal subarachnoid hemorrhage (SAH) is a life-threatening neurological emergency caused by a ruptured brain aneurysm leading to extravasation of blood into the subarachnoid space (the space between arachnoid membrane and the pia mater, the meningeal layers that protect the brain). Aneurysm is enlargement of the blood vessel wall due to weakness of the wall itself (1) . SAH accounts for 5-10% of all strokes, affecting relatively young age leading to premature loss of productive life years. The overall incidence of SAH is about 9 per 100,000 person years (2). The incidence of the disease increases with age. The mean age at presentation of SAH is 50 years (3), but the younger population (<50 years) still account for a substantial portion of those affected (4, 5). Mortality rates secondary to SAH has been reported to range from 30-50%, leaving the rest of patients with different degrees of disability (6-8). Devastatingly, the vast majority of deaths are common within 2 weeks after the bleed and 10% of deaths occur before hospital arrival (2). The disease places a financial burden on health care system as result of hospitalization in the first year after the ictus where two-third of the costs are generated (9). Neurological and medical complications are common following SAH and contribute significantly to patient outcomes. Emergency medical and surgical interventions of the condition and effective prevention of the complications contribute to better patient outcomes.

1.1.1.2 Etiology

The main cause of SAH in 80-85% of the cases is ruptured intracranial aneurysms. Other etiologies of SAH (15-20%) include perimesencephalic hemorrhage, arteriovenous malformation, dural arteriovenous fistula, arterial dissection, mycotic aneurysms, trauma, bleeding disorders such as

sickle cell disease and cocaine use (10). Aneurysms are acquired lesions that occur in 1-2% of population (11, 12). They are also known as saccular aneurysms because of their shape which look like a berry like shape. Proximal arterial bifurcations are the main location of aneurysms in the circle of Willis with 85% of these aneurysms being found in an anterior location (12). Arteries commonly affected by aneurysms include: the junction between anterior communicating artery and the anterior cerebral artery, the middle cerebral artery, the internal carotid artery, the basilar artery, the posterior cerebral artery, and the vertebral artery as shown on **Fig 1.1** (12, 13). The definite mechanism of aneurysms development and growth is unknown, however, there are known modifiable and non-modifiable risk factors for developing aneurysms. Non-modifiable risk factors include having a family history of first-degree relatives diagnosed with SAH and heritable connective-tissue disorders such as polycystic kidney disease, the Ehlers–Danlos syndrome (type IV) and pseudoxanthoma (14-16). One study has found that family history is a strong risk factor for SAH with adjusted odds ratio (3.32, 95% CI, 1.54 –7.12) (17). In addition, race, and sex differences in SAH risk exist. Black people have a risk of 1.2 times higher than that of white and women also have a risk of 1.2 times that of men for SAH development (18). Modifiable aneurysm risk factors include: active smoking, hypertension, use of sympathomimetic drugs (e.g. cocaine use), and alcohol abuse (14, 19).

1.1.1.3 Presentation

Headache is the hallmark symptom for most patients presenting with SAH (20). It is usually described by patients as “the worst headache they experienced in their life” (21). The headache onset is acute in nature and quickly intensifies within a manner of seconds. Up to 40% of patients experience warning leak or sentinel headache (22). This sentinel headache occurs 2 to 8 weeks prior to SAH ictus (23, 24). The sentinel headache might be misdiagnosed as migraine or other

types of headache; as a result, the mortality and morbidity in patients with misdiagnosed sentinel headache is four-fold higher than those who had their headache correctly diagnosed in initial evaluation (25). Other signs or symptoms of SAH presentation include nausea and/or vomiting, focal neurologic deficits, loss of consciousness, photophobia and neck stiffness (26). In addition, 27% of patients present with seizures (27).

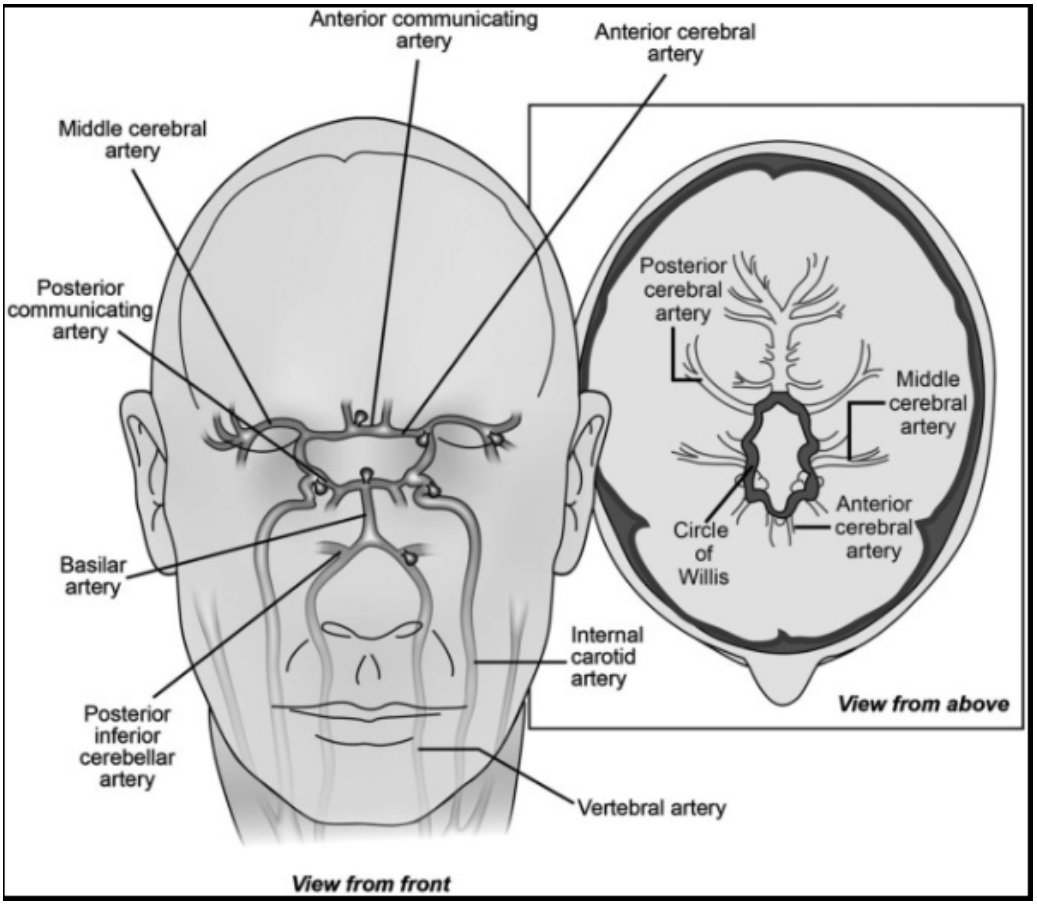

Figure 1-1: Common sites of intracranial saccular aneurysms. Copied from Williams and Brown, (13).

1.1.1.4 Diagnosis

When there is a clinical suspicion of SAH suggested by the history and physical exam, patients need to be referred to well equipped specialist centres for diagnosis. Several diagnostic modalities are used for the diagnosis and are discussed below.

1.1.1.4.1 Computed tomography (CT)

CT scan is the first imaging procedure performed in patients presenting with their worst headache with clinical suspicion of SAH diagnosis. High quality CT scan done as early as the first initial 12 hours after the presentation can detect 100% of the cases and more than 93% within 24 hours of symptoms onset (28). CT scan also reveals any other abnormalities such as the presence of intraparenchymal hematomas, hydrocephalus and cerebral edema (29). CT scan sensitivity for detection SAH decreases over time as red blood cells degradation happens and this can lead to normal findings despite the history of SAH presentation (10).

1.1.1.4.2 Lumbar puncture (LP)

LP is used for detection of blood in the cerebrospinal fluid. It is the second step of diagnosing SAH if CT scan results show no blood or an alternate cause for symptoms. If there is no indication of increased intracranial pressure, LP is performed. Up to 20% of SAH cases have negative CT scan findings (30). However, there is a controversy of performing the LP due to the challenge of distinguishing the blood from SAH from that of the trauma that can happen at the time of lumbar puncturing (31). Furthermore, post-LP headache could occur in up to 38% of the patients undergoing an LP (32).

1.1.1.4.3 CT angiography (CTA)

CTA is the standard tool for anatomical study of the aneurysm and for treatment planning after plain CT confirms SAH. Due to its wide availability and non-invasiveness, CTA is routinely performed if an aneurysm is suspected. The CTA identifies aneurysm's location, size, and relationship to the parent blood vessel, surrounding vessels and other anatomical structures. The sensitivity of CTA has ranged from 97%-199%. Despite its high sensitivity, CTA cannot identify the cause of bleeding in up to 30% of patients (33-35).

1.1.1.4.4 Digital subtraction angiography (DSA)

DSA is the gold standard tool for diagnosis of the vascular etiologies of SAH with 99% sensitivity and confirming aneurysmal obliteration (36-38). It is invasive, expensive, time consuming and have higher risk for complications than CTA (34, 39, 40). DSA remains the standard care in examining patients with cerebral aneurysms where the initial CTA is negative. DSA supplements CTA in SAH management and guiding the choice of aneurysm treatment (surgical clipping vs. endovascular coiling) (41-43).

1.1.1.4.5 Magnetic resonance imaging (MRI)

The sensitivity of MRI to SAH was reported to increase with time (e.g. over few days post ictus) in contrast to the CT scan where the sensitivity decreases as time interval from hemorrhage increases (44). Scanning time is longer than CT, making MRI less suitable for some patients such as those who are confused or restless upon presentation. MRI is beneficial in subacute and chronic cases of SAH where the sensitivity is superior to CT (44, 45).

1.1.1.4.6 Transcranial Doppler ultrasonography (TCD)

A hand-held Doppler transducer is placed on the cranial skin to determine the velocity and pulsatility of the blood flow in basal cerebral arteries. TCD has been frequently utilized in the evaluation of cerebral vasospasm that follows SAH. TCD is easily employed in critical care setting because it is non-invasive, and it does not involve using contrast dye agents and it has lower cost than other available procedures. Elevated blood flow velocity in TCD indicates vasospasm while DSA is performed to confirm it (46, 47).

1.1.1.5 GRADING OF SAH

Several radiological and clinical grading systems are reported in patients with SAH. The most well-known grading scales are Hunt and Hess Scale, Glasgow Coma Score, World Federation of Neurological Surgeons Scale and Fisher Scale.

1.1.1.5.1 Clinical grading

1.1.1.5.1.1 Hunt and Hess classification of SAH

This classification was most frequently used in early years due to easy classification and the abundance of this scale in neurosurgical literature (48, 49) (**Table 1-1**). Hunt and Hess scale has been the most dependable scale in practice. One of the limitations of this scale is that some of high-grade patients may show an improved outcome in their Glasgow outcome Scale (GOS). In addition, patients who fall into one single scale could have different outcomes (50). This phenomenon can be explained by the fact that the admission circumstances of the patients cannot provide a whole prediction of the patient outcome and there might be other components missing from the grading that could contribute the outcome. The modified version of Hunt and Hess Scale

includes grade 0 for unruptured aneurysms and grade 1a for those causing neurological deficits but lacks the evidence of rupturing aneurysms (51).

1.1.1.5.1.2 Glasgow Coma Score (GCS)

Initial development of GCS as a tool of examining level of consciousness after head trauma goes back to (Teasdale and Jennett 1974) who selected an assessment on three axes system (eye, motor and verbal) (52). Severity of brain dysfunction and coma can be assessed after 6 hours of head trauma (**Table 1-2)** (48). The benefit of this scale is that it is easily used by health professionals such as nurses and physicians for patient's neurological functional assessment and it is commonly used for research purposes in head trauma (53, 54). A strong correlation exists between good GCS and favourable outcomes measured by Glasgow Outcome Scale has been reported (55).

Table 1-1: Hunt and Hess classification (48)

Grade	Description
1	Asymptomatic or mild headache
2	Cranial nerve palsy and moderate to severe headache, nuchal rigidity
3	Focal neurologic deficit, confusion, lethargy
4	Stuporous, hemiparesis, early decerebrate posture
5	Comatose, decerebrate rigidity, morbid appearance
One point is added for associated systemic illnesses that may include: HTN, DM, atherosclerosis, COPD, or documented severe vasospasm	

COPD, chronic obstructive pulmonary disease; DM, diabetes; HTN, hypertension

Table 1-2: Glasgow Coma Scale Components (48)

Eye opening	Best verbal response	Best motor response
		6: obeys commands
	5: oriented	5: localizes
4: spontaneous	4: confused	4: withdraws
3: to speech	3: inappropriate words	3: abnormal flexion
2: to pain	2: incomprehensible sounds	2: extension
1: none	1: none	1: none
	TOTAL GCS SCORE: 3-15	

GCS, Glasgow Coma Score

1.1.1.5.1.3 World Federation of Neurological Surgeons (WFNS) Grading of SAH

WFNS was developed in 1988 for classification of patients with SAH and it gained worldwide use and acceptance (48, 56) (**Table 1-3**). This scale utilizes GCS for determining the level of consciousness and it combines focal neurologic functioning of the patients for prediction of disease severity and patient outcomes (57). WFNS grades 2 and 3 have same GCS but the difference is the absence and presence of focal neurologic deficits. WFNS is a strong predictive system which has shown consistency in predicting poor outcomes with higher grades but there is no evidence of providing definite difference between single scores (50, 58). Modified WFNS was proposed by Japan Neurosurgical Society where grades 2 and 3 were graded as GCS of 14 and 13 respectively, regardless of the neurological status (59).

Table 1-3: WNFS Grade (48)

WFNS Grade	Glasgow Coma Scale Score	Motor Deficit
1	15	Absent
2	14-13	Absent
3	14-13	Present
4	12-7	Present or absent
5	6-3	Present or absent

1.1.1.5.2 Radiological assessment

1.1.1.5.2.1 Fisher Grading Scale

Fisher scale was proposed in 1980s. Fisher scale predicts the risk of development of vasospasm depending on the amount and the distribution of the blood on CT scan (**Table 1-4**) (60). A clear correlation has been reported between thick subarachnoid blood (≥1 mm) in fissures and vertical cisterns and the incidence of severe vasospasm (60). However, two studies have reported a non-significant correlation of Fisher grading with the development of symptomatic vasospasm (60, 61). As a result, Modified Fisher Scale has been proposed based on weakness in how the Fisher Scale handled patients with Grade 4. Grade 4 in Fisher Scale includes patients with intracerebral hemorrhage (ICH) or interventricular hemorrhage (IVH) only if there is diffuse or focal SAH. Modified Fisher Scale assigns score 1 no thick clot in the cisternal or bilateral IVH, 2, if bilateral IVH, score 3, thick cisternal clot and 4 if both thick clot and IVH (62). The Modified scale has superior prediction value than Fisher Scale for symptomatic ischemia from vasospasm (62).

Table 1-4: Fisher Grading Scale (60)

Fisher Scale	Blood on CT
1	No SAH identified
2	Diffuse or vertical layers <1 mm thick
3	Localized clot and/or vertical thickness >1 mm
4	Intracerebral or intraventricular hemorrhage

CT, computed scan; SAH, subarachnoid hemorrhage

1.1.1.6 Complication of SAH

1.1.1.6.1 Medical complications

Hyponatremia is far the most common electrolyte imbalance in SAH patients, and the incidence of hyponatremia has been reported to range from 30%-56% (63-65). Hyponatremia has the definition of serum sodium concentration level <135 mEq/L; and severe if serum sodium < 131 mEq/L (66). Hyponatremia is caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH), exogenous vasopressin administration (63, 67) and cerebral salt wasting syndrome (CSW) due excess production of natriuretic peptides which lead to an excessive natriuresis (66). Disproportionate fluid therapy and diuretic use can also contribute to hyponatremia (68). Hyponatremia predisposes patients to worse outcomes such as increased risk of seizures and neurological impairment (68-70). This is in addition to volume contraction which could lead to greater risk of developing vasospasm and delayed ischemic deficit (64, 69-71). In addition to electrolyte abnormalities, about 3 out 4 patients have hyperglycemia on admission. The mean blood glucose levels of patients admitted within 72 hours from SAH diagnosis is

approximately 9 mmol/L (72, 73). Blood glucose > 7.2 mmol/L was associated with altered cognition and levels > 8.4 mmol/L has been associated with neurologic deficit (74). Few studies have found that hyperglycemia persists with levels above 7 to 8 mmol/L in the first 1 or 2 weeks (73, 75). A study has recently found that patients with persistent hyperglycemia are at seven-fold higher risk of having poor outcomes than normoglycemic ones, but there was no such association between isolated hyperglycemia and clinical outcome (76). Another study has found three-fold increase of poor outcomes in hyperglycemic patients with SAH (72). Fever, defined as body temperature >38.3°C, is another common medical complication that is seen in patients with aneurysmal SAH (77). About 70% of patients have post-operative fever and about 50% are non-infectious (78). Fever unfavourably affects the patient outcomes and predisposes the patients to acute ischemic stroke (79, 80). Also, fever leads to the development of delayed cerebral ischemia and angiographic vasospasm (79, 81). It has been suggested that fever might be a component of the systemic inflammatory response to SAH, detrimentally exposing the patients to worse outcomes (82).

1.1.1.6.2 Rebleeding

Rebleeding after the initial SAH has been reported to occur in < 4% of patients during the first day after the initial ictus (83). In a recent literature review investigated the rebleeding after SAH in 43 articles has reported that the 4% occurrence reported in old studies is underestimated. Ultra-early rebleeding, which is rebleeding that occurs within 24h of the initial bleed was estimated to be as high as 9-17% and the timeline of the rebleeding in most cases appeared to be within 6 hours (84). Rebleeding significantly affects the prognosis and it is a major cause of morbidity and mortality (85). The mortality reaches up 80% in patients who rebleed after the initial SAH (86). Substantial contributors of increasing risk of rebleeding include the timeline of rebleeding occurrence, high

systolic blood pressure, disease severity (low GCS and poor Hunt-Hess grade), intracerebral or intraventricular hematoma, thickness of the hemorrhage, number of aneurysms and location, early angiography, evidence of sentinel headache, hyperglycemia and degree of platelet sensitivity (87).

1.1.1.6.3 Hydrocephalus

Acute hydrocephalus is a common complication following SAH. It has been reported that 15-87% of patients experience acute hydrocephalus after SAH (74). Exacerbation of patients' medical condition from acute hydrocephalus warrants drainage of the cerebrospinal fluid (CSF) which often improves the clinical condition of the patients (88-91); however, the risk of unfavourable outcomes tends to be higher in those presenting with acute hydrocephalus (91). Chronic hydrocephalus is seen only in a small proportion of the patients (74).

1.1.1.6.4 Seizures

Seizures following SAH is a well-recognized complication that is observed in patients after the ictus. Although there are variations in seizure rates in the literature due heterogenicity of patient populations and differences in practices of prescribing prophylactic agents, reports have estimated that up to 28 % of the patients develop seizure after SAH (79-81). Pathophysiologic mechanisms of post SAH seizures involve acute biochemical dysfunction and delayed reorganization of gliotic cells (25). Poor grade SAH, intracerebral hemorrhage, ruptured aneurysms involving in the anterior circulation, loss of consciousness in the initial presentation, the amount of blood in the subarachnoid space, age <40 years are among the risk factors for seizures following SAH (65, 82). Furthermore, the type of aneurysm treatment has also been reported to influence seizure development. Endovascular coiling is associated with less risk of seizures incidence compared to surgical clipping (83, 84). Some studies have linked poor outcomes with seizures following SAH

(85). Seizures following SAH were associated with neurologic impairment, decreased cerebral blood flow, and increased incidence of delayed ischemic neurological deficits, and increased intracranial pressure (25). Hospital mortality was also significantly higher in patients with seizures (80).

1.1.1.6.5 SAH-induced vasospasm

SAH-induced vasospasm has been the most single important cause of morbidity and mortality occurring after SAH (92). Vasospasm is defined as angiographically visible cerebral arteries narrowing after aneurysmal SAH. Terms used to refer to vasospasm include angiographic vasospasm, radiographic vasospasm, and arterial narrowing. Despite successful treatment of the ruptured aneurysm and removal of the rebleeding risk, up to 50% of the patients received the treatment experience a syndrome of focal and/or cognitive deficits as a result of cerebral vasospasm that occurs in between 4^{th} and 9^{th} days post SAH and the risk disappears over a period of 2-4 weeks (93, 94). An onset time of 3 days after SAH with the peak period at 6-8 days has also been reported (95). Angiographic vasospasm is common in 70% of the patients (96-98) while symptomatic vasospasms occurs in 20-40% (97, 98). The lack of good understanding of the mechanisms that play a role for the development of vasospasm impeded effective prevention and management of vasospasm. Presence of oxyhemoglobin from the SAH blood leads to many deleterious events that damage the endothelial cells, disrupting the normal autoregulation of the vascular tone. Possible pathologic mechanisms elucidated to be responsible for the cerebral vasospasm include direct oxidative stress on the smooth muscle cells (SMCs), increase production of endtheline-1 (ET-1), decrease in nitric oxide (NO) production (93). To start with the oxidative stress, the damage in the endothelial wall of the blood vessels leads to activation of small molecules such as Rho kinase, G-proteins, and protein kinase C (PKC) (99). Those substances can further

activate various enzymes ultimately resulting vasoconstriction. One of those enzymes is ras homologous (Rho) GTPases. (Rho) GTPases activates Rho kinase which phosphorylates Rho A. Rho A then directly phosphorylates myosin light chain (MLC) resulting the binding of actin to the phosphorylated myosin light chain. This binding leads vascular smooth muscle contraction. Caldesmon is a regulatory protein that detaches actin from MLC by phosphorylation. This protein is also inhibited by Rho kinase and Rho A through activation of PKC subunits prolonging the biding of the action and myosin light chain (contraction of the smooth muscle cells) (**Figure 1-2)** (93, 100). In addition to this, the imbalance between the vasoconstrictors (e.g.,endothelin-1) and vasodilators (e.g., nitric oxide) of the blood vessels contributes to vasoconstriction. Increase endothelin-1 (ET-1) and decrease in nitric oxide causes vasoconstriction. ET-1 binds to ET receptors leading to activation of variety of second messengers that activate SMC contraction **(Figure 1-3)** (93, 100). On other hand, the decrease in nitric oxide production leads to vasoconstriction due to reduction in secondary messenger named cyclic guanosine monophosphate (cGMP) which in turn inhibits the dephosphorylation of MLC ultimately leading to impaired vasodilatation (93).Regardless of its mechanism, vasospasm is poorly understood; however, the prediction of vasospasm is enhanced due admission CT scan and Fisher Scale grading that can provide a rough prognosis of patients who are at high risk for vasospasm (101).

1.1.1.6.6 Delayed Cerebral Ischemia (DCI)

DCI is the most important cause of morbidity and mortality in patients who survive the initial bleed. Its characterized by delayed neurological deterioration and focal deficits that can progress to brain ischemia. DCI occurs in up to 30% of patients 3–14 days post aneurysmal SAH (102, 103). Similar terminologies of DCI include delayed ischemic neurological deficit (DIND), delayed

ischemic deficit (DID). There is inconsistence in defining DCI in literature. The latest agreed proposal definition of DCI in 2010 by a multidisciplinary group of experts is the "Occurrence of focal neurological impairments (such as hemiparesis, aphasia, apraxia, or neglect) or decrease of at least 2 points on GCS that last for at least 1 hour and is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT, MRI, and other lab studies" (102, 104). In the past, DCI was considered to occur as a result of narrowing cerebral vessels due to vasoconstriction that leads to brain infarction, however, there is a mounting evidence that DCI can be caused by several underlaying factors and several pathological mechanisms beyond vasospasm have been elucidated. Those mechanisms include abnormalities in microcirculation, imbalance in fibrinolytic system, micro-thrombosis, inflammation, and apoptosis. To start with cerebral vasospasm which is believed to be the most common related pathway for DCI, cerebral vasospasm affects both the microvascular and macrovascular circulations. Studies have shown that there is decrease in cerebral perfusion prior to infarction in those who develop DCI (105, 106), which made it a sensible therapeutic target to increase cerebral blood flow using various modalities such induced hypertension, hypervolemia, and balloon angioplasty. Presence of SAH blood triggers many vasculo-pathological changes that interfere with normal blood vessel autoregulation including an imbalance between vasodilators (NO) and vasoconstrictors (ET-1) as explained in **Figure 1-3,** as well as inflammation and injury of endothelial cells due to oxidative stress. The concept that vasospasm is the contributor of DCI due to decreased cerebral blood flow guided many trials to target angiographic vasospasm. A randomized, double blinded, placebocontrolled trial entitled "Clazosentan to overcome neurological ischemia and infarct occurring after subarachnoid hemorrhage" or CONCIOUS trial has been conducted with the aim to investigate the endothelin receptor antagonist (clazosentan) to

prevent vasospasm after SAH (107). CONCIOUS-1 trial has confirmed that clazosentan significantly reduced the incidence of moderate to severe vasospasm, however, the trial CONCIOUS-2 investigated the functional outcome of clazosentan defined as reducing vasospasm-related morbidity and mortality. Unfortunately, this trial showed no significant difference in functional outcome or vasospasm-related morbidity and mortality (108). These findings supported that vasospasm is not the only contributor of DCI and there are other factors that play role in pathological development of DCI and affect the outcomes in patients with aneurysmal SAH.

Abnormalities in microcirculation have also been reported to involve the pathology of the DCI as these alterations occur at the small arterioles and capillaries levels that are radiologically invisible. Studies on animals have revealed constriction in intraparenchymal and pial arterioles suggesting that microcirculation dysfunction plays a role in decreased cerebral blood flow and possible DCI development (109, 110). Cerebral blood flow depends on cerebral autoregulation and neurovascular coupling where both of these fundamental functions are impaired in SAH. Under physiologic conditions, release of glutamate from local neurons activates metabotropic glutamate receptors on astrocytes leading to increased end foot Ca+ which in turn triggers releasing vasodilatory substances that induce vasodilation. Experimental animal model studies have revealed that this neurovascular coupling evoked vasodilation was inverted in SAH animal models where neuronal activation still lead to increase in Ca+ in astrocyte end foot but evoked transient or sustained vasoconstriction rather than vasodilation (102, 111, 112). This microvascular spasm can possibly have profound impact on delivery of oxygen and nutrients to brain parenchyma and is implicated in DCI development (102, 113). Impaired nitric oxide and endothelial NO synthase are one of the main signaling pathways thought to involve microvascular constriction (114).

Micro-thrombosis has also been related to development of DCI. Blood coagulation markers levels have been reported to increase after SAH. Neurological function can be impaired by formation of microthrombi. Development of procoagulants such as platelet-activating factors have been documented on the 4th day after SAH (115). Von Willebrand factor (primary initiator of coagulation) levels elevate as early as 72h after SAH (116) which is the timeframe prior to vasospasm and DCI occurrence. Loss of regulation of coagulation and fibrinolytic system has been reported (117, 118). Moreover, presence of micro-embolic signals has been shown by a prospective study in up to 70% of patients using TCD and there was a trend towards an association between the micro-embolic signals and clinical vasospasm but this was not statistically significant (119). Giller et al have also reported detection for micro-emboli in patients undergoing routine TCD monitoring. Nine out of 11 patients (82%) who have the micro-emboli developed ischemia confirmed by the presence low-density areas on their CT scans (120). The micro-emboli formation and their correlation with cerebral infarction is an area of interest for possible cause of DCI. It can be the reason of developing DCI for patients who have not had vasospasm, or it can enhance the risk of developing DCI for those who experienced vasospasm but there is no such strong correlation between micro-embolic and DCI development and that supports the idea that DCI is caused by many pathophysiological inter-related pathways.

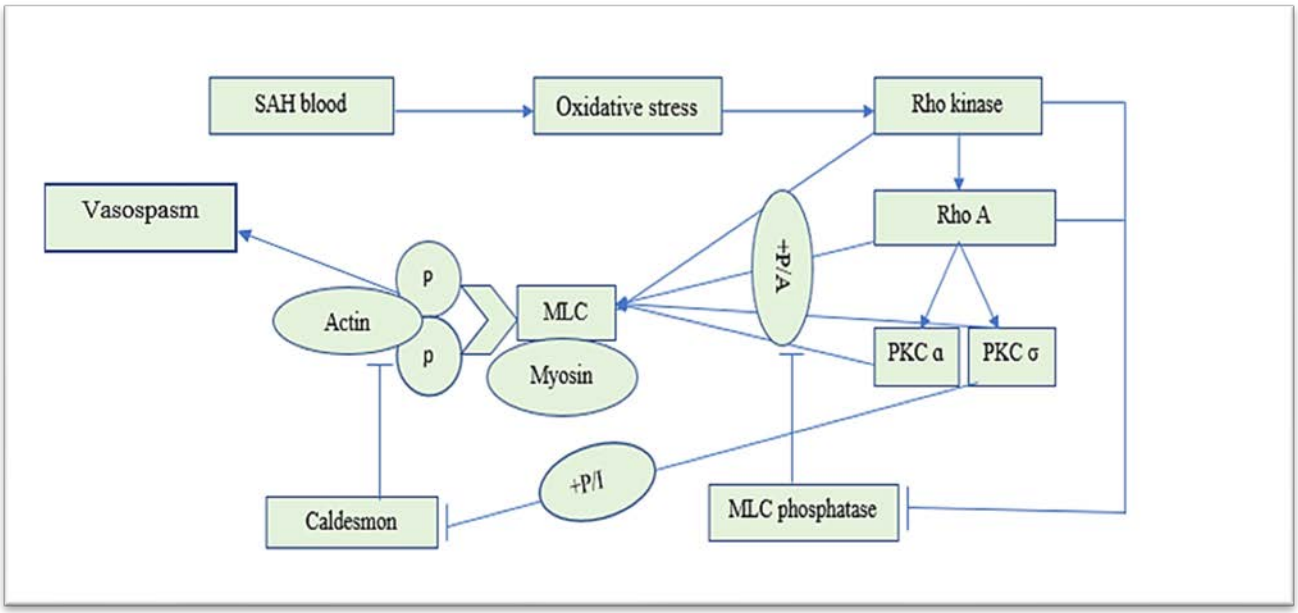

Figure 1-2: Rho kinase and Rho A dependent mechanism of vascular smooth muscle contraction. Rho kinase activates Rho A, both Rho kinase and Rho A phosphorylate myosin light chain (MLC) and enable binding of actin to MLC, resulting vascular smooth muscle contraction. Rho kinase and Rho A also inhibit MLC phosphatase, and this prolongs the phosphorylated form of MLC. Rho kinase and Rho A activate Protein kinase (PKC) subunits α and σ, where both subunits contribute activation of MLC by phosphorylation. PKC σ also inhibits a regulatory protein (caldesmon) that detaches actin from MLC by phosphorylation.

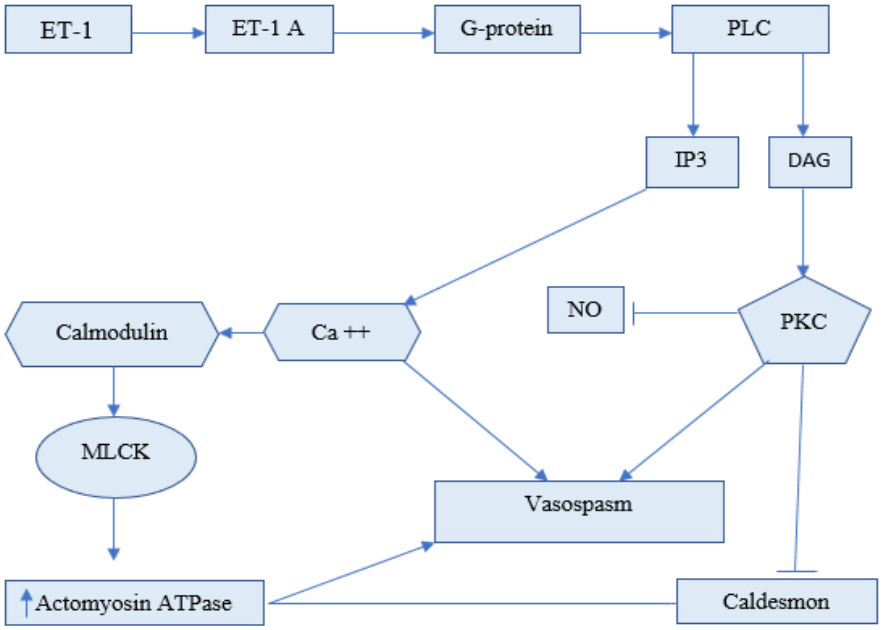

Figure 1-3: Signal transduction cascade of vasoconstrictor endothelin -1 (ET-1) via endothelin-1 A receptor (ET A). Endothelin is released from endothelial cells as result of the shear stress, presence of CO2, O2, oxyhemoglobin and ischemia. ET-1 produce vascular smooth cell contraction by activation ET A receptor. ET A is a G protein-coupled receptor that in turn activates phospholipase C (PLC). Activation of PLC lead to hydrolysis of phosphatidylinositol-4, 5-bisphosphate to diacylglycerol. (DAG) and inositol-1, 4,5-trisphosphate (IP3). IP3 activates Ca+ release from sarcoplasmic reticulum. Calcium/calmodulin dependent myosin light chain kinase (MLCK) phosphorylates myosin light chain facilitating actin to bind myosin. Diacylglycerol (DAG) subsequently activates protein kinase C(PKC) in which in turn inhibits caldesmon by phosphorylation, caldesmon is a regulatory protein that dissociate actin from myosin light chain complex. PKC also inhibits nitric oxide production (NO). All these signal transduction lead to vascular smooth muscle contraction (vasospasm).

Fibrinolytic cascade dysfunction can also play role in DCI pathophysiology. Under physiologic condition, plasmin degrades the fibrin clot under regulation of tissue plasminogen activator (t-PA) which converts plasminogen into active plasmin. The reverse of the fibrinolysis is achieved by activation of plasminogen activator inhibitor-1 (PAI-1). Imbalance of fibrinolytic cascade has reported to correlate with DCI. Study reported that PAI-1 is detected more in cerebral spinal fluid of patients with DCI and higher levels of PAI-1 in the CSF associate with vasospasm and poor outcome (121). Furthermore, inflammatory processes are involved in DCI development and in turn brain insult. There is a growing interest in research towards inflammation following SAH. SAH induces systemic proinflammatory processes that lead to recruitment of peripheral immune cells such as granulocytes and macrophages to brain parenchyma by chemoattractant and adhesion molecules like selectins on endothelial cells and leucocytes where they release cytokines (82, 122-124). Patients with DCI has been reported to have increased levels of sP-selectin. The expression of sP-selectin is also stimulated by cytokines such tumor necrosis α (TNF)-α leading to leucocyte adhesion (118). Matrix metalloproteinase 9 (MMP9) increase is also reported in SAH animal models (125). The MMP9 helps to degrade the tight junction and membrane proteins of extracellular facilitating the immune cells to reach the brain by crossing the blood brain barrier (126). Neutrophils and macrophages appear in the subarachnoid space within hours and they initiate activation of the microglia and astrocytes (127, 128). The key role of neutrophils is phagocytosis of the red blood cells in subarachnoid space followed by degranulation and death. Migration of macrophages and microglia to the site of injury led to ongoing inflammation in the brain. Both neutrophils and macrophages are detected in the CSF after SAH (128, 129). Also, activation of immune cells after SAH leads to secretion of inflammatory mediators including cytokine, chemokines and reactive oxygen species (ROS). TNF-α increase in early phases of SAH

and it is responsible for variety of inflammatory cascade activation and regulation of other cytokines, immune cell function and apoptosis (130-132). The elevation of these cytokines is correlated with brain damage. TNF-α up-regulation in post SAH has been reported in both animal model (133, 134) and patients (131, 132, 135). TNF-α inhibition can be useful therapeutic target for brain injury following SAH. Several pro-inflammatory mediator expressions are also upregulated following SAH, these include (IL)-6, 1L-1ß. IL-6 is significantly increased in CSF after SAH (136, 137).

1.1.1.7 Management of SAH

1.1.1.7.1 Management overview

All patients who present with SAH are considered emergent cases and evaluated carefully regarding their respiratory and cardiac function levels. Once the stabilization is ensuring, the patients are transferred to neurologic critical care units to maximize and facilitate their further care and monitoring. The goal is to secure the ruptured aneurysm and to prevent rebleeding and complications such as vasospasm and DCI. Blood pressure normalization with antihypertensive drugs such labetalol and nicardipine is permissible and, if needed, hypertension is allowed after aneurysm treatment to maintain adequate blood supply to the brain (138). Also, managing hyperglycemia is crucial to prevent poor outcomes (75). The American Heart Association (AHA) guidelines recommend that volume contraction to be treated with crystalloid or colloid fluids (Class IIa, Level B evidence) and avoidance of administration of large volumes of hypotonic fluids and intravascular volume contraction (Class III; Level of Evidence B) (74). Many SAH patients present with fever in the course of the disease due to inflammation reaction or loss of central temperature control and associated with worse outcomes. Current guidelines of AHA indicate

aggressive treatment and effective temperature management, although this recommendation is a low to moderate grade evidence but high with expert opinion (8, 74). Analgesics such narcotics are indicated for pain management. Deep venous thrombosis (DVT) is relatively common post SAH due to immobilization of patients particularly those with poor mental status (74). DVT prophylaxis by sequential compressive devices followed unfractionated heparin or low molecular weight heparins once the aneurysm is secure is a routine general measure for SAH management (74).

1.1.1.7.2 Aneurysm management

Randomized trials have proven that securing the ruptured aneurysm is safe and reduces the risk of re-rupture (139-141). Treatment can be done by either surgical clipping or endovascular coiling at high-volume centers (142). Surgical clipping is an invasive procedure that involves surgical opening of the skull (craniotomy) and exposing the aneurysm and then placing a titanium clip across the neck of the aneurysm to close the sac while maintaining the normal blood flow through the adjacent normal arteries. Endovascular coiling is a minimally invasive technique that is done by inserting a micro-catheter into the femoral artery via an initial catheter. The microcatheter tip has a platinum coil is attached to and up on reaching the lumen of the aneurysm, an electric current is applied to dissociate the coil from the microcatheter. The coil remains there and forms a clot that stops the bleeding and prevents re-rupturing. Endovascular coiling has favourable outcome at 1 year compared to the surgical clipping, however, coiling is not the best option for all aneurysms because it cannot eliminate intracerebral hemorrhage or the mass effect of massive aneurysms. Clipping showed higher rates of aneurysm obliteration, longer durability, and reduced retreatment over the endovascular treatment (140, 141).

1.1.1.7.3 Management of complications

1.1.1.7.3.1 Rebleeding

Early intervention of ruptured aneurysm can mitigate the risk of rebleeding (92). AHA Guidelines suggest controlling the blood pressure after SAH and until aneurysm obliteration with titratable antihypertensive agents like nicardipine while balancing the hypertensive-related rebleeding and cerebral perfusion (Class I; Level of Evidence B). Although there is no agreeable range or limit defined for keeping the blood pressure, the AHA guidelines recommend reducing the systolic blood pressure to <160 mm Hg (Class IIa; Level of Evidence C) (74). In cases where aneurysm intervention is delayed and there is a huge risk of rebleeding, short term treatment (<72h) with tranexamic acid or aminocaproic acid is acceptable with evidence of no medical contraindication (Class IIa; Level of Evidence B) (74)

1.1.1.7.3.2 Hydrocephalus

Drainage is done by either inserting an external ventricular drain (EVD) or lumbar drain (74). Its use is controversial because it increases risk of rebleeding compared to lumbar drainage. One study reported an increased risk of rebleeding with EVD (143) and others found no such association (90, 91). Chronic hydrocephalus is managed by permanent cerebrospinal fluid diversion (ventricular shunt placement) (74). Shunt dependency was reported to be positively correlated to severity of the disease (144) and little is known whether there is a difference in developing chronic shunt - dependent hydrocephalus between patients treated with surgery and those who underwent endovascular treatment. One study has found no difference between the two treatments in later development of chronic shunt- dependent hydrocephalus (144).

1.1.1.7.3.3 Seizures

The benefits of using prophylactic antiepileptic drugs (AED) after SAH remains debatable. An association of AED use and the incidence of poor outcome have been reported by several recent studies (100, 101, 145). Incidence of radiographic vasospasm, neurologic deterioration, cerebral infarction, and elevated temperature during the hospital stay were reported (100). AHA guidelines suggest that prophylactic anticonvulsants may be used in immediate post-hemorrhagic period (Class IIb; Level of Evidence B). The AHA guidelines are against routine use of anticonvulsants (Class III; Level of Evidence B), but in cases with high risk for delayed seizure disorder, anticonvulsants might be considered (Class IIb; Level of Evidence B) (74).

1.1.1.7.3.4 SAH-induced vasospasm and DCI

Prevention of vasospasm and DCI is the key element for post SAH complication management. AHA guideline recommend that a fixed dose of oral nimodipine to be administered within 96 hours from ictus to all patients regardless of their weight, age, disease severity, comorbidities, and other patient-specific characteristics and to be continued for 21 days (Class I; Level of Evidence A) (6). Another modality for vasospasm management has gained a widespread acceptance is “triple-H therapy”, induced hypertension, hypervolemia, and hemodilution. It is indicated for patients who developed vasospasm to prevent delayed cerebral ischemia. It has been reported that hypervolemic hypertensive therapy led to successfully reversal of neurological deterioration from angiographic vasospasm of some patients (145). An other study (Awad et al) has also reported that hypervolemia and hemodilution therapy in clinical vasospasm can lower the mortality and morbidity of patients from SAH-induced cerebral vasospasm (146). Despite the utilization of triple H therapy, the efficacy is ambiguous and its not devoid of potential complications. Medical complication that are associated with triple H therapy include pulmonary edema, myocardial ischemia, hyponatremia,

cerebral hemorrhage, and cerebral edema (147). Because of these complications, euvolemia is recommended, instead. Endovascular angioplasty as well as intra-arterial administration of vasodilators may be reasonable options for those with refractory symptomatic vasospasm as AHA guideline recommend (Class IIa; Level of Evidence B) (6).

1.1.1.8 Conclusion

Aneurysmal SAH is a life-threating medical condition caused by a ruptured brain aneurysm. The mortality and morbidity rates of the disease are high. SAH affects relatively young age leading to premature loss of productive life. There are many complications that follow SAH, however, the main contributors of poor outcome are cerebral vasospasm and DCI. The mechanisms that lead to those two complications are poorly understood. Various interconnected pathways have been reported to implicated in development of cerebral vasospasm and DCI. The only therapeutic intervention available to prevent vasospasm and DCI is nimodipine which will be detailed in section **1.1.2**.

1.1.2 Nimodipine

1.1.2.1 Nimodipine overview

Nimodipine (±) is a dihydropyridine calcium channel blocker with greater selectivity for cerebral blood vessels than other agents within the same class (148, 149). Animal studies (dogs, cats, rabbits, goats, and monkeys) of nimodipine reported an increase in cerebral blood flow after nimodipine use (150, 151) . Comparing nimodipine to other dihydropyridine such as (lercanidipine, manidipine), nimodipine is the most powerful dilator at nanomolar concentrations in pial arteries (150, 152). Nicardipine has been studied. Large, controlled trial of nicardipine showed that it did not improve patient outcome at 3 months although it reduced the delayed ischemic deficit and angiographic vasospasm (153). Likewise, verapamil is not selective towards cerebral blood vessels and even using topical (inter-arterial) verapamil raises a controversy of possible hemodynamic effects (154). Nifedipine has also been reported not to reverse the vasospasm in canine model (155).Taking all together, nimodipine is the most effective, selective and relatively less hemodynamic changes available (150, 154). As a result, nimodipine has been tested in the setting of aneurysmal subarachnoid hemorrhage (SAH) to prevent cerebral vasospasm and delayed cerebral ischemia (DCI). Nimodipine is the only pharmacological agent that has been shown to improve neurological outcomes following SAH by several randomized clinical trials (156-159).

1.1.2.2 Randomized clinical trials of oral nimodipine therapy in patients with subarachnoid haemorrhage

1.1.2.2.1 Allen et al.1983

The first double-blinded randomized clinical trial investigating the efficacy of nimodipine in preventing ischemic neurologic deficits from cerebral vasospasm (159). The study was designed based on previous findings of nimodipine animal experiments (159-161). Patients included in the

study aged 15-80 years old and nimodipine was started within 96 hours from ictus. Patients presented with neck stiffness, fever, photophobia, drowsiness were excluded. Patients had to be oriented at least to places, people and year to be eligible. Diagnosis of aneurysm by CT scan, CSF evaluation and DCA on admission was required. Nimodipine gelatin capsules were used in the trial and those who were not able to swallow the capsule, the liquid of the capsule was drained and delivered through nasogastric tubes. The starting dose of nimodipine was 0.7 mg/kg followed by 0.35 mg/kg every 4h for 21 days. Randomization was stratified according to centre, surgeon, or group of surgeons. Intracranial surgeries were done after nimodipine administration for 24h and within 14 days from entry of the trial. No other antispasmodic agents were given during the study. Detailed neurologic examination was mandatory at the start of treatment and within 7 days of the end of the 21 days period. Neurological evaluation was performed daily in patients and whenever a deficit occurred, full examination was done including CT scanning and intracranial angiography. Eligibility and the outcome of the study were confirmed by double-blinded committee composed of neurosurgeons, neurologists and neuroradiologists. Radiological assessment was based on modified classification of the amount of blood in the subarachnoid space (Grade 1-4) ranking from least to highest amount of blood. Degree of spasm in percentage has been also evaluated comparing the diameters of the artery at time of deficit to that of pre-entry. The primary end point of this study was the occurrence of ischemia neurologic deficits and classification of the deficits in to normal, mild-moderate, and severe after 21 days. The study enrolled 125 patients, 121 met the study criteria, 5 patients from the 121 patients were further excluded due to protocol violation. Finally, 116 patient's data were included the study findings. Sixty patients were in the placebo arm and 56 patients in the nimodipine arm. For clinical outcome, 8/60 patients in placebo group and 1/56 patients had severe outcome (p <0.03). In addition, 7 patients died in placebo arm compared to 3

patients in nimodipine arm. Plasma and CSF nimodipine concentration measured in 6 patients were 6.9 ± 4.9 ng/ml and 0.7 ± 0.34 ng/ml, respectively. This is an indication that nimodipine crossed the blood brain barrier (BBB) and reached the site of its action. In conclusion, the study suggested that nimodipine protects patients from poor outcome and recommended patients with normal neurologic function to start nimodipine and continue the treatment for 3 weeks (159).

1.1.2.2.2 Philippon et al.1986

The primary objective of the study was to confirm the findings of the previous RCT (Allen et al.1983) that nimodipine reduces the severity of neurologic deficits associated with vasospasm (157). The participants of the study were ages between 15-65 years old presented with SAH within 72 hours from aneurysm rupture. The patients were Grades 1, 2, and 3 of Hunt and Hess grading Scale and did not have complications such as hydrocephalus, intracerebral hematoma, or comorbidities such as hypertension, and abnormalities in cardiac, liver, kidney function. Also, patients who underwent an operation prior to day 4 and those who were not treated with nimodipine were excluded from this trial. The dose of nimodipine used in Philippon et al was 60 mg every 4 hours for duration of 21 days. No other vasodilators or ß-blockers were used in the study. The participants underwent complete neurologic evaluation at the beginning and at the end of the trial and upon observation of any deterioration by CT, CSF, and angiography. All patients had angiography on admission and on day 6 (before the surgery) or any time neurologic deficit occurred. The study endpoints were the occurrence of vasospasm and neurologic deficits. Vasospasm frequency, intensity, and extension was examined. The neurologic outcome was assessed by using GCS and classified as good, for Scales I and II, severe for III and IV, and dead. Results from 70 patients included in the study (39 patients treated with placebo and 31 with nimodipine) showed that neurologic deficit was seen in 29 patients (74.4%) of placebo group and

18 cases (58.1%) of nimodipine group, but this was not statistically significant. Deficits secondary to vasospasm were documented as 11 cases in placebo group (28.2%) versus 4 cases (12.9%) in nimodipine arm. Only 2 in nimodipine group had sever deficit from spasm or died compared to 10 cases in placebo group (p <0.05). Vasospasm was detected in 14 and 25 (3 post-operation) cases in nimodipine and placebo group, respectively. Although the difference is observable, but it was not statistically different. The severity of the spasm between the two groups was not significantly different. Patients who were categorized as moderate and severe vasospasm outcome were 23 % and 29%, respectively, in nimodipine arm while in the placebo, 36% of patients had moderate spasm and 33% developed severe spasm. This trial confirmed the effectiveness of nimodipine in reducing the frequency of vasospasm although this was not statistic significant in the study. Also, nimodipine significantly reduced the incidence of sever outcome (157). These results are in agreement with Allen et al findings (159).

1.1.2.2.3 Petruck et al.1988

This was multicenter double-blind placebo-controlled trial conducted in seven Canadian centers. University of Alberta was the organizer of the trial. It involved enrollment of poor grade patients (Hunt and Hess Grades 3 or above). The previous Allen et al (159) and Philippon et al (157) results of effectiveness of nimodipine in reducing the poor outcome were from trials conducted on good grade patients (i.e. lower disease severity). Petruck et al. study was designed to provide precise confirmation of nimodipine efficacy for preventing large vessel vasospasm in patients with higher blood volume in subarachnoid space since those patients are at greater risk of spasm than the good grade patients (156). The participants of the trial were aged 18 years or older and had aneurysmal SAH within 96 hours confirmed by the CT scan, LP, and angiography. Patients underwent neurological status assessment and those who were not oriented to person, city, or place in at least

two different instance more than 30 minutes apart were enrolled. No other calcium channel blockers were allowed. The dose of nimodipine was 90 mg of nimodipine gelatin capsule or placebo every 4 hours and the drug to be started before the operation (within 96 hours) of SAH onset). Patients who could not swallow the capsule, the liquid content was drawn and administered through nasogastric tubes. Repeat angiogram was done on the 8th day post SAH and CT scan was repeated at 3 months assessment for all patients. Neurological examination was performed at admission, end of the 21 days of treatment, and after 3 months. The three primary end points of the study were: first, reduction in worse outcome resulted from delayed ischemic deficits secondary to spasm; second, reduction in development of moderate diffuse and severe diffuse vasospasm in 8th day from SAH; and third endpoint was difference in the incidence and size of hypodense areas on 3 months follow up CT scans. The results came from the analysis of 154 patients (82 patients treated with placebo and 72 with nimodipine). For 21 days and 3 months outcome determined by GOS, the number of patients with good outcome was statistically greater in the nimodipine group at 21 days ($p < 0.05$), and at 3 months ($p < 0.001$). Subgroup analysis by SAH grades was also conducted. The findings of this study clearly reported the effectiveness of nimodipine in Grades 3 and 4 but Grade 5 did not show better outcome in ischemic deficits from vasospasm in nimodipine treatment.

1.1.2.2.4 Pickard et al.1989

Four centers participated in the British aneurysm nimodipine trial. This study was designed to investigate the effect of nimodipine on ischemic deficits, cerebral infarction, and outcome at 3 months in patients with SAH (158). Patients participated in the study were 18 years or older, admitted for subarachnoid hemorrhage within 96 and treated with nimodipine soon after the ictus. SAH diagnosis was confirmed by CT or LP. Patients who were pregnant and those with

comorbidities such liver, renal, cardiac, and previous recent SAH were excluded from the trial. The dose of nimodipine was 60 mg every 4 hours for 21 days. Patients who were able to swallow the tablets were given as tablets and those who were unable to swallow the tablets were crushed and delivered through nasogastric tubes. Clinical grading of patients was based on GCS and were graded from (I-V). Special attention was given to assess patient's consciousness, focal neurological features, and symptoms resulted from ischemia or other cause. The deterioration was defined to be appearance of focal sign or decline one point from GCS existing more than 6 hours determined by CT, LP, or necropsy. Data of 552 patients were reviewed (276 placebo, 276 nimodipine) at 3 months post SAH. This trial reported a significant reduction of cerebral infarction in the nimodipine group compared to placebo (22 vs 33%, respectively). Similarly, poor outcome, defined as dead, vegetative state, or severe disability) was significantly reduced by 40% following nimodipine treatment. Nimodipine clearly reduced the incidence of cerebral ischemia and the poor outcome as reported by other RCTs.

1.1.2.3 Physicochemical properties of nimodipine

Nimodipine, 3-O-(2-methoxyethyl) 5-O-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, has 1,4-dihydropyridine ring structure (**Figure 1-4**). Nimodipine is a yellow crystalline compound that is insoluble in water but soluble in ethanol, polyethylene glycol 400 and dimethyl sulfoxide (162). Nimodipine is a basic drug with pka 5.41 (163). It is sensitive to light with a degradation half-life of 56 hours and 16 hours when 50 ng/ml nimodipine solution was exposed to day-light and ultra-violet light, respectively (164). Nimodipine is a chiral compound with an asymmetric carbon at position 4 and it is marketed as a racemic mixture of (+)-R and (-)-S nimodipine. Towart et al have found that (-)-S nimodipine is approximately twice as potent vasorelaxant as the racemic mixture; however, the clinical relevance

of such differential pharmacology is unclear (165). Nimodipine is highly lipophilic drug (log P = 3.41) . Its selectivity towards cerebral blood vessels has been attributed to the drug's increased lipophilicity and its ability to cross the blood-brain barrier (163)

The biopharmaceutical classification system (BCS) lists nimodipine as Class II depending on solubility and permeability of nimodipine. Nimodipine exhibits low solubility and high permeability (163, 166).

1.1.2.4 Nimodipine pharmacodynamics

Nimodipine inhibits the influx of calcium ions through voltage-gated L-type calcium channels of vascular smooth muscles, thereby, causing vasorelaxation (151, 167). Nimodipine has been shown to dilate blood vessels and prevent vasoconstriction particularly in small arterioles whose diameters are 70-100μm (168, 169). Despite that, nimodipine reported benefits in SAH patients were not related to its effects on vasospasm suggesting other potential mechanisms. Furthermore, nimodipine elevates adenosine levels in the central nervous system with subsequent inhibition of the excitatory neurotransmitter glutamate, a potential neuroprotective mechanism (170-173) .

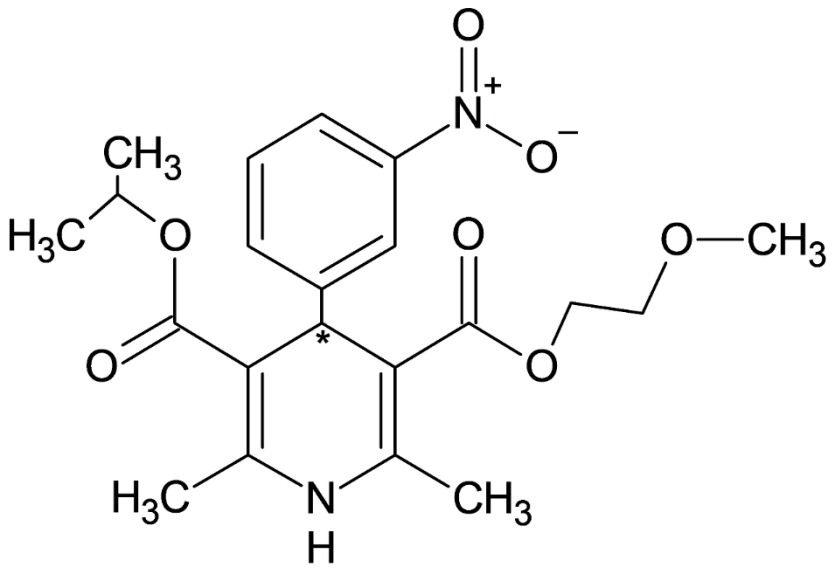

Figure 1-4: Chemical Structure of nimodipine *, Chiral carbon

1.1.2.5 Nimodipine pharmacokinetics

1.1.2.5.1 Absorption

Nimodipine undergoes rapid absorption from the gastrointestinal tract followed by extensive first-pass hepatic metabolism. The oral bioavailability of nimodipine has been reported to range from 3 to 30%. Both the parent drug and the metabolites start to circulate 10-15 minutes after ingestion with time to peak concentration (T_{max}) ranging from 0.5-1 h (174, 175). Nimodipine follows a linear PK profile where the area under the concentration-time curve (AUC) is proportional to the administered dose within approved dosing range.

1.1.2.5.2 Distribution

Steady state volume of distribution (Vd) of IV nimodipine ranges from as low as 0.94L/kg to as high as 2.3 L/kg while the average of that in central compartment is 0.43 L/kg (176) Nimodipine

is highly bound to plasma proteins (>95%) particularly, alpha-acid glycoprotein (AAG)(177). Therefore, the distribution of nimodipine can be affected by the concentration of AAG. To illustrate, Woodward et al. compared AAG levels in SAH patients with controls before and after surgery.(177) Preoperative values of AAG in SAH patients were 39% higher than the values of controls. However, AAG concentration of patients declined significantly postoperatively and reached control levels 48 hours post-surgery. This transient shift in AAG concentrations had an impact on serum nimodipine total concentration and the unbound fraction. Furthermore, the total concentration of nimodipine in cerebrospinal fluid was inversely proportional to the concentration of AAG (177). It is worthy to mention that this study did not measure the concentration of AAG in CSF of SAH patients and it is possible that AAG levels increase in CSF for some disorders that affect the brain such as multiple sclerosis (MS) where patients have high levels of AAG in the brain (178). Elevated AAG in the brain might be the interpretation of the lack of correlation between CSF drug concentration and unbound concentration reported in Woodward et al (177).

1.1.2.5.3 Metabolism and excretion

Nimodipine undergoes extensive hepatic metabolism with cytochrome P450 (CYP3A4 and 3A5) enzymes (174, 175, 179). It undergoes multiple metabolic pathways (**Figure 1-5**) and more than 18 metabolites have been reported (180, 181). The clearance of nimodipine is variable and reported to be 0.84 L/kg per hour in healthy volunteers while that of SAH patients recorded as 1.18 L/kg per hour (176). Nimodipine plasma concentrations decline rapidly with a half-life of 1.2-1.8 hours after intravenous infusion (176). After oral dosing, an elimination half-life of 5-10 hours have been reported (164, 176, 182, 183). Since nimodipine has a chiral carbon atom, it exists as (+)-R and (-)-S enantiomers. The (-)-S enantiomer is more rapidly eliminated than (+)-R following oral

dosing (184-187). On the other hand, such differential effect was not apparent when nimodipine was administered intravenously, suggesting enantioselective first pass metabolism. In human, the major metabolites are formed from ring dehydrogenation (dehydro-nimodipine) by CYP3A4 (188). Other main metabolite is from an oxidative demethylation (189). 50% of the dose is excreted in urine and 30% in bile mainly as metabolites (176) .

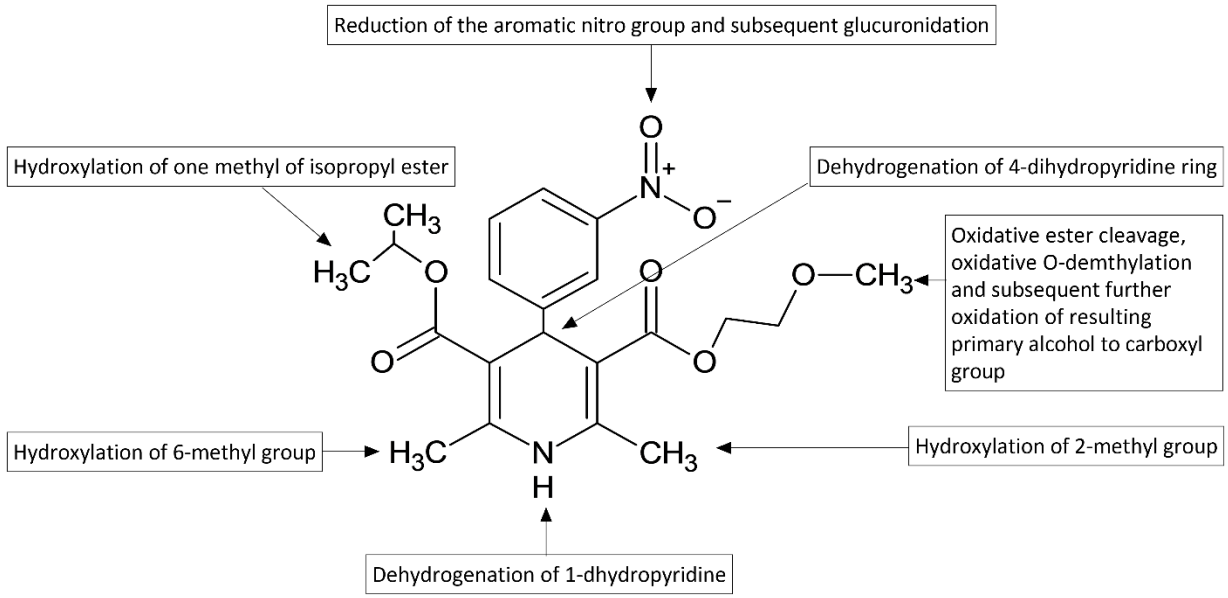

Figure 1-5: Common biotransformation reaction of nimodipine

1.1.2.6 Nimodipine pharmacokinetic variability

A large interpatient variability in nimodipine pharmacokinetics has been reported in different patient populations and healthy volunteers. Variabilities in the bioavailability (F) and clearance (CL) of nimodipine with resultant altered nimodipine concentrations were reported. **Figures 1-6-1-8** summarize observed nimodipine concentrations in various pharmacokinetic studies. As seen in **Figure 1-6**, steady state plasma concentrations following intravenous infusion (C_{ssivi}) ranged from as low as 9 up to 73 ng/ml with equivalent daily dosing. Similarly, a wide range of peak plasma concentrations following oral administration (C_{maxPO}) following a single 60 mg dose (**Figure 1-7**) and at steady state (**Figure 1-8**) was observed. Patient-specific factors that had an influence on PK parameters are age and sex of the participants, comorbidities, variabilities in metabolism due to genetic polymorphism and more. This section provides a summary of the potential covariates contributing to alterations in nimodipine PK parameters.

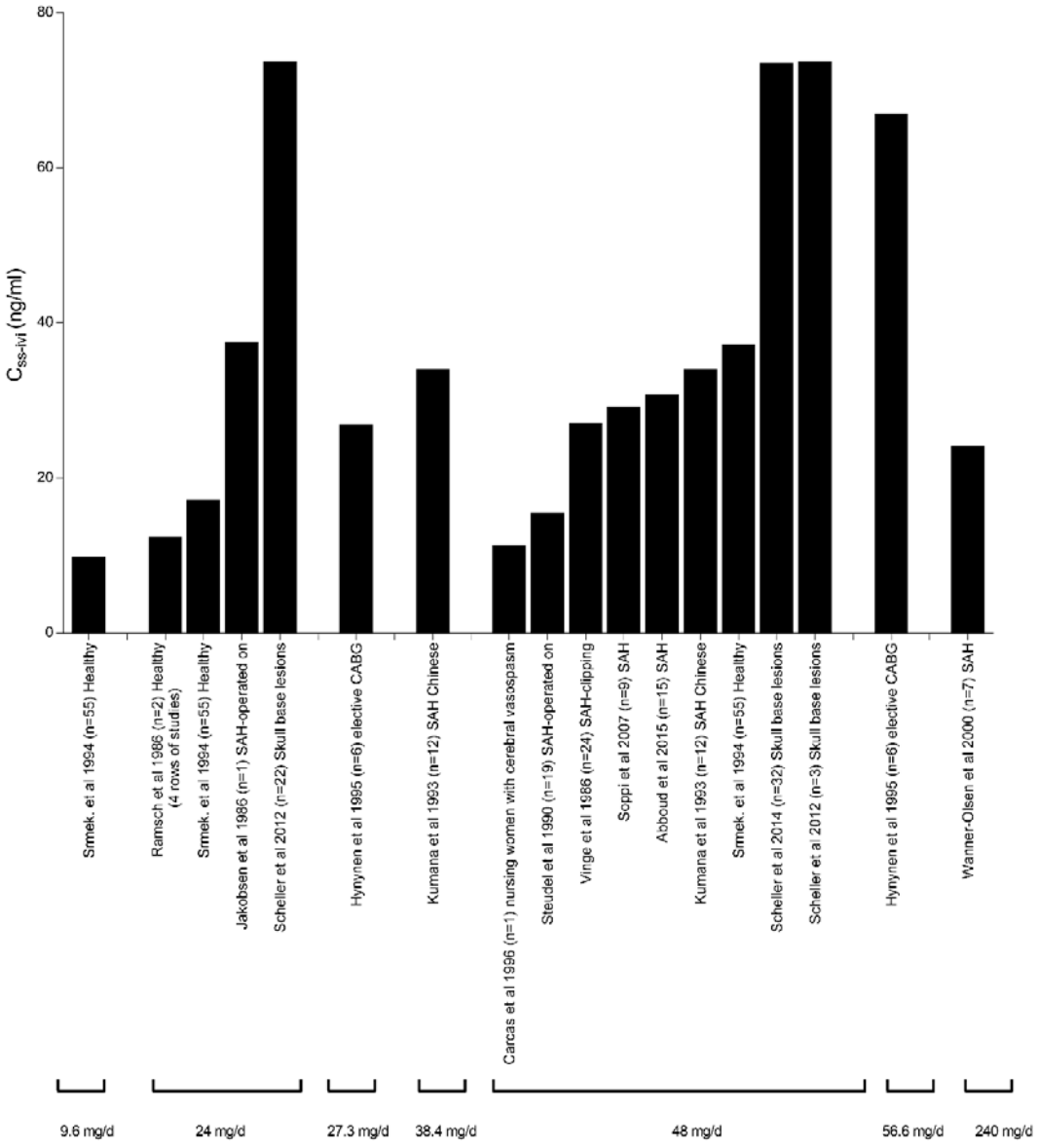

Figure 1-6: Steady state nimodipine plasma concentrations following intravenous infusion (C_{ssivi}) in healthy individuals, patients with SAH, skull base lesions, cerebral vasospasm and subjects underwent coronary artery bypass grafts (CABG) (187, 190-201). In Scheller et al 2012 (n=22), patients started on 1mg/h for 2 hours, increased to 2mg/h, then decreased to 1mg/h due to low blood pressure. The duration that patients was on 2mg/h was not reported in the article. The data for this study is grouped under a daily dose of 24 mg (196).

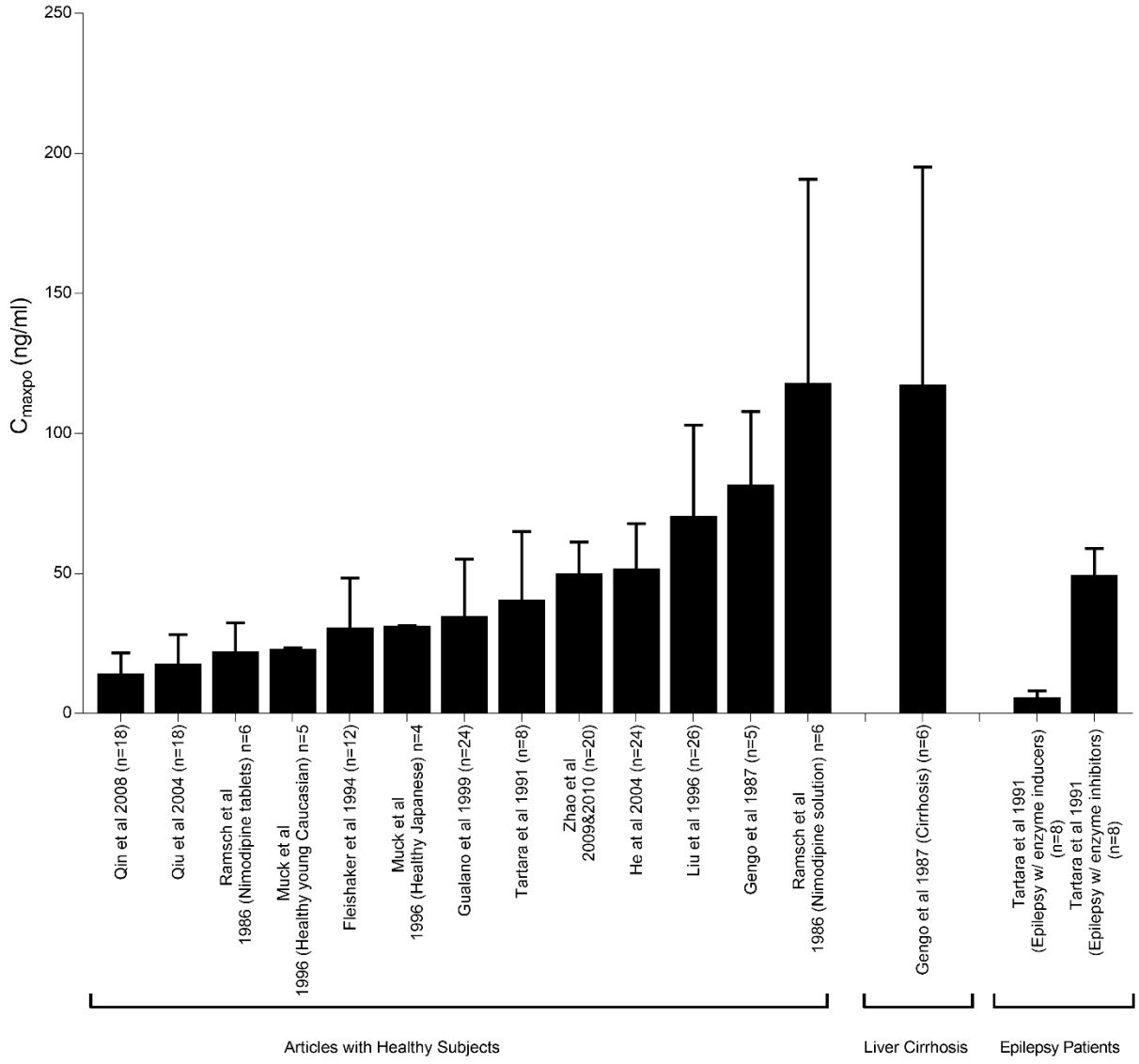

Figure 1-7: Peak plasma concentrations following oral administration (C_{maxPO}) following administration of a single 60 mg nimodipine dose healthy individuals and patients with liver cirrhosis and epilepsy (190, 195, 202-212)

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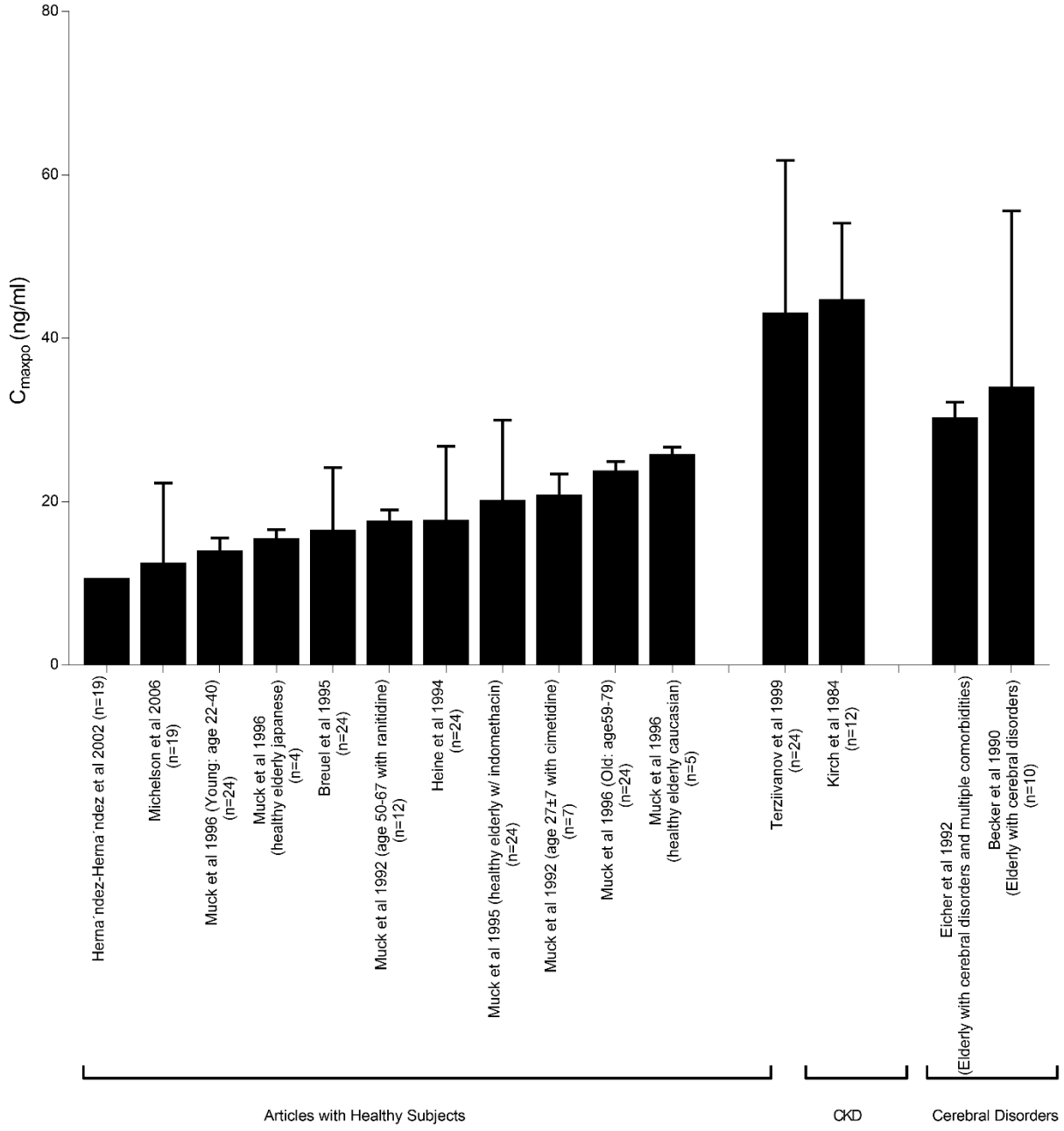

Figure 1-8: Steady state peak plasma concentrations following oral administration of nimodipine 30mg being administered orally every 8 hours in healthy individuals, patients with chronic kidney disease (CKD) and subjects with cerebral disorders (183, 185, 207, 213-221)

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1.1.2.6.1 Effect of age on nimodipine pharmacokinetics

Muck et al specifically compared the PK parameters of nimodipine in young versus old population. Young age group included 24 subjects aged 22-40 years and the older age group included 24 subjects aged 59-79 years. The study showed no statistically significant differences in PK parameters between the two groups after a single IV infusion of 15µg/kg infused over one hour. However, a higher C_{max} and AUC was observed at the old age group when both groups were administered nimodipine 30mg orally as a single dose and as a three times daily multiple-dose regimen. The reported C_{max} and AUC for the old group were 23.3±1.62 ng/ml and 47.5±1.62 ng*h/ml, respectively; while for the young group C_{max} and AUC were 13.5±2.03 ng/ml and 25.7±1.73 ng*h/ml, respectively (222). This suggests that older adults have reduced first pass metabolism of oral nimodipine compared to younger patients. Similar C_{max} and AUC values has been reported in a study of 21 elderly patients with various central nervous system disorders (223). In addition, in a population pharmacokinetic analysis of previous PK studies, the authors have found that nimodipine CL was reduced by 32% in elderly subjects (≥ 65yrs). Furthermore, the authors reported a significant inter-individual variability of nimodipine PK parameters: 60% in CL, 59% in apparent volume of distribution of the central compartment and 95% in apparent volume of distribution of the peripheral compartment (182).Similar to what was observed in healthy subjects, there was also a negative correlation between nimodipine CL and age seen in 24 SAH patients treated with surgical clipping ($r = -0.4$, p value < 0.05) (224). Taken together, nimodipine first pass metabolism and clearance are age dependent.

1.1.2.6.2 Effect of sex on nimodipine pharmacokinetics

Sex differences in nimodipine pharmacokinetics were not as apparent as the effect of age. Results from Muck et al have reported that nimodipine CL after IV infusion among males is slightly lower than females the young and elder males clearance were 0.84 L/h/kg and 0.58 L/h/kg , respectively while that of young and elder females were 1.18 L/h/kg and 1.10 L/h/kg, respectively)(222). On the other hand, there was no sex differences (*p* value 0.573) in the observed nimodipine levels a study involving SAH patients (225).

1.1.2.6.3 Effect of renal function on nimodipine pharmacokinetics

The influence of renal function on oral nimodipine (30 mg administered every 8 hours) has been studied in two reports (226, 227). In both studies, C_{maxPO} was at least 17 ng/ml higher in chronic kidney disease (CKD) subjects compared to those with normal kidney function (**Figure 1-8**). Kirch et al have concluded that nimodipine half-life is prolonged in patients with CKD, defined as eGFR < 60ml/min. However, both groups were not age matched, where patients in the CKD group were older (65.3±4.1 vs. 25.2±2.4 years), which could have contributed to this observation. Furthermore, Terziivanov et al have reported increased nimodipine PK variability among patients with CrCl 51-80ml/min. The authors concluded that although nimodipine is mainly metabolized by the liver, renal function could be an additional factor contributing to nimodipine PK variability.

1.1.2.6.4 Effect of liver disease on nimodipine pharmacokinetics

Since hepatic metabolism is the main route of nimodipine elimination, the influence of liver cirrhosis on nimodipine PK has been studied. It has been reported that the apparent oral clearance of nimodipine is substantially lower in liver cirrhosis patients than in healthy subjects. As a result, the observed C_{maxPO} in patients with liver disease was 1.4 to 9-fold higher than C_{maxPO} observed in

those with normal liver function (**Figure 1-7**). Furthermore, there was a large variability in the influence of liver disease on nimodipine oral clearance with CL ranges from as low as 60 L/h to as high as 652 L/h. Like other highly protein bound lipophilic compounds that are extensively metabolized, the observed variability may be due to disease-induced changes in protein binding, gastric and enterohepatic circulation, and hepatic blood flow, as well as intrinsic decrease in the metabolic capacity of the liver (203). The clinical significance of decreased nimodipine clearance in cirrhosis patients was evidenced by a reduction in main arterial pressure in cirrhotic patients. A concentration-related blood pressure reduction was seen in the individual data of cirrhotic patients, which was not seen in control subjects (203).

1.1.2.6.5 Effect of genetic polymorphism on nimodipine pharmacokinetics

As discussed under "Metabolism" nimodipine is mainly metabolized by CYP3A enzyme family. Genetic polymorphism of the enzyme CYP3A5 has been reported to alter the disposition of nimodipine. In a pharmacogenetic study conducted in healthy Chinese individuals, participants who were carriers of homozygous CYP3A5 (*3/*3) and received oral nimodipine had higher C_{max} and AUC compared to those with heterozygous CYP3A5 (*1/*3) or wild type CYP3A5 (*1/*1). This has been attributed to reduced nimodipine CL in the homozygous CYP3A5 (*3/*3) group (538±153 vs. 758±260 L/h, *p*-value = 0.03) (212).

1.1.2.6.6 Drug interactions and nimodipine pharmacokinetics

Being a substrate of CYP3A enzymes, nimodipine is susceptible to drug-drug interactions with liver microsomal enzymes inducers (such as phenytoin and carbamazepine) and inhibitors (such as cimetidine and grapefruit juice). Since SAH patients often present with seizures, interactions with antiepileptic drugs are of most relevance. Effects of enzyme-inducing AEDs like phenytoin,

carbamazepine, and phenobarbital were investigated in epilepsy patients. After a single oral dose of 60 mg nimodipine, patients who have been taking enzyme-inducing AEDs for at least 4 months had a significantly lower nimodipine plasma concentrations compared to healthy controls (C_{maxPO} 4.2 vs 39 ng/ml, respectively) (228). Similarly, in a study involving SAH patients, concomitant administration of phenytoin in two patients resulted in lower nimodipine concentrations compared to those not on phenytoin (229). On the other hand, epilepsy patients taking enzyme inhibiting AEDs such as valproic acid had a slightly higher nimodipine plasma concentrations compared to normal subjects (C_{maxPO} 48 vs 39ng/ml, respectively) (228). It is not clear; however, if altered nimodipine concentration translates into altered drug response. To illustrate, administration of cimetidine and grapefruit juice with nimodipine resulted in 75 and 51% increase in AUC of nimodipine, respectively. However, there were no significant differences in blood pressure despite the increase in AUC (220, 230). Several studies have also reported no interactions when nimodipine was co-administered with ranitidine, clazosentan, tirilazad, diazepam, propranolol, and indomethacin (202, 220, 222, 231-233).

1.1.2.6.7 Influence of nimodipine formulations on nimodipine pharmacokinetics

Nimodipine is marketed as soft gelatin capsule, oral tablet, intravenous solution and oral suspension. Both tablets and capsules have comparable AUCs (91.1 ng.h/ml and 103.5 ng.h/ml, respectively). However, CmaxPO is lower with tablet formulation compared to the capsule (45.6 ng/mL vs. 69.1 ng/mL, respectively) and T_{max} is longer with tablets (0.77 h vs 0.59 h). This suggests that the tablet formulation has slightly delayed absorption compared to the capsule. There was no direct comparison of nimodipine oral liquid to other oral formulations. Nimodipine capsules and oral liquid are dosage forms available in US while nimodipine IV solution is used only in Europe. In North America, IV solution is not used due to severe adverse effect

(hypotension). In Canada, the tablet form is the only available formulation. Nimodipine tablet has the following non-medicinal ingredients: Crospovidone, ferric oxide yellow, hypromellose, macrogol, magnesium stearate, maize starch, microcrystalline cellulose, povidone, and titanium dioxide (234) .

1.1.2.6.8 SAH characteristics and nimodipine exposure

The effects of SAH severity and occurrence of DCI on nimodipine pharmacokinetics have been explored in few studies. Hunt and Hess score and World Federation of Neurological Surgeons Grade are used to grade SAH severity on a scale of 1-5, where 5 is the most severe SAH. Four PK studies have reported SAH grades (194, 225, 229, 235). Following intravenous administration of nimodipine, it appears that there is no correlation between SAH grade and C_{ssiv}. However, following oral administration, poor-grade patients had significantly lower C_{max} and AUC values than those observed in good-grade patients. This suggests that the observed differential effects of SAH grade could be attributed to reduced nimodipine bioavailability secondary to administration via feeding tube rather than altered drug clearance. Further studies are needed. With regards to DCI, three patients developed DCI in a study involving 24 SAH patients. All subjects were treated with clipping and were administered IV nimodipine for 7 days. The three patients that developed DCI had plasma nimodipine concentrations similar to patients who did not. Authors concluded that it seems unlikely that the therapeutic failure could be attributed to individual deviations in the pharmacokinetics of the drug (224). However, the study was underpowered to detect such differences.

1.1.2.6.9 Conclusion

Nimodipine has been shown to improve outcomes following SAH. Guidelines recommend that all patients receive a fixed dose of oral nimodipine for 21 days. However, pharmacokinetic studies have reported extensive variability of nimodipine concentrations in SAH. The observed variability may have been attributed to practice variations in nimodipine administration, disease severity, administration of concomitant interacting drugs and cytochrome P450 polymorphism. It is not clear if minimal systemic exposure to nimodipine results in changes relating to drug's clinical benefit and contributes to worsening patient outcomes. Further studies are needed to determine if such association exists and if there is a need for nimodipine dosage individualization in SAH patients.

1.2 Rationale

Guidelines recommend that all patients presenting with aneurysmal SAH should receive a fixed dose of oral nimodipine 60 mg every 4 hours for 21 days from SAH onset regardless of weight, age, disease severity, comorbidities, and other patient-specific characteristics (8). Pharmacokinetic studies have reported extensive variability of nimodipine concentrations in various populations (**Figures 1-6, 1-8**) and in the setting of SAH, with some patients had undetectable nimodipine plasma levels (190, 194, 198, 200, 225). The observed variability in nimodipine exposure may have been attributed to practice variations in nimodipine administration, disease severity, administration of concomitant interacting drugs, presence of food in the gut, and cytochrome P450 polymorphism (187, 210, 236, 237). While previous randomized controlled trials have found that nimodipine reduces the incidence of poor neurologic outcomes (defined by death, persistent vegetative state, and severe disability) by 40-86%, still up to 22 % of patients in the nimodipine arm experienced poor outcomes (156, 158, 159). Therefore, it is not clear if all patients are getting

the full benefit of nimodipine using a fixed dose regimen and the evidence supporting a correlation between nimodipine concentrations and patient outcomes is scarce and not clear. Riva et al. have reported an association between nimodipine CSF concentrations and neurological outcomes at 9 months following SAH onset but they were unable to find such correlation with plasma concentrations (238). It should be noted, however, that all patients were dosed using nimodipine IV infusion and their plasma concentrations ranged from 24.9 to 71.8 ng/ml, concentrations way above what has been reported in some patients given oral dosing (174, 198). Nevertheless, it is not clear if minimal systemic exposure to oral nimodipine affects on its benefit in SAH patients and contributes to worsening patient outcomes. Intravenous nimodipine was compared to the oral route in two small, randomized trials (239, 240). Both studies have found no difference in patient outcomes; however, the number of patients with high Hunt and Hess grade (IV and V) was small to draw conclusions on the comparability of both routes in high grade patients. Further research is needed. SAH patients who are able to swallow will administer the whole capsules or tablets, otherwise, nimodipine liquid needs to be drawn from the capsules, tablets to be crushed or commercially available liquid to be administered through enteral feeding tubes for those who are unable to swallow, such as those with altered mental status or mechanically ventilated. It is not clear, however, whether these techniques of administration are equivalent. Few studies have shown a decreased nimodipine AUC and increased PK variability when it is administered via feeding tubes. To illustrate, Soppi et al have reported nimodipine concentrations following the standard 60mg po Q4H dosing schedule in SAH patients (198). Nimodipine maximum concentrations ranged from as low as 1 ng/ml up to 56.7 ng/ml for those receiving tablets and 0.9-1.7 ng/ml for those receiving an extemporaneously prepared oral suspension. Similarly, Abboud et al compared plasma nimodipine concentrations administered parenterally followed by enteral administration.

The AUC of the parenteral route was significantly higher than that of the oral route. Moreover, nimodipine AUC for those who swallowed whole nimodipine tablets was higher than those who received it through enteral feeding tube [median 52 (IQR 26–1411) ng.h/ml vs. 23 (IQR 6-1272 ng.h/ml), respectively, *p*-value 0.006] (190) In addition, two patients with high grade SAH had undetectable nimodipine concentrations. Similarly, Kumana et al. have reported reduced exposure to nimodipine in a patient given crushed tablets through gastric tube (241). The reason for this reduced bioavailability is unclear. In vitro experiments indicated that adsorption of nimodipine by the nasogastric tubing was limited (< 20 %) and that was unlikely to have been the cause of a low plasma concentration (242). Further studies are needed to examine the impact of nimodipine administration through feeding tube on outcomes in SAH patients.

Nimodipine is a chiral compound that exists as a racemic mixture. Towart et al have found that S(-)-nimodipine is approximately twice as potent as the racemic mixture (169). Nevertheless, most of the assay methods in the literature for nimodipine did not consider the chirality of the molecule and did not separate the two enantiomers. Stereochemistry is a crucial knowledge to incorporate in the growing laboratory analytical methods and it is extremely important to emphasize the significance of using enantioselective assays when measuring the effectiveness, determining side effect profiles, or studying the disposition of chiral therapeutic agents. Three methods have been reported for enantioselective assay of nimodipine. However, the reported methods were time-consuming, involved multistep extraction procedures and required large sample volumes (243-245). Therefore, there was need for enantioselective assay which is simple and involve one step liquid-liquid extraction to determine nimodipine in human plasma by using liquid chromatography (LC) with chiral stationary phase (CSP) column and tandem mass spectrometry (MS/MS).

1.2 Overall hypotheses

After adjusting for disease severity, the odds of experiencing poor outcome (delayed cerebral ischemia and vasospasm) in patients who receive nimodipine through feeding tube is different from those who swallowed the whole tablets. In our pilot study, we hypothesize that nimodipine exposure ($AUC_{0\text{-}4h}$) will be lower in SAH patients who experienced poor outcomes compared to those who experienced favourable outcomes. In addition, age, nimodipine administration technique (oral vs. via feeding tube) will be identified as potential factors contributing to the observed nimodipine systemic exposure.

1.3 Objectives

Overall objectives of the thesis were:

- To investigate the effect of different nimodipine administration techniques (feeding tube vs oral) on patient outcomes. This objective was achieved by conducting a retrospective chart review study. The primary aim of the study was to investigate the impact of nimodipine administration through enteral feeding tubes, in the first 7 days from onset, on the outcomes in patients with SAH. We chose the first 7 days of exposure as the onset of vasospasm and DCI are generally within that time period. In addition, the secondary aim was to determine the impact of nimodipine mode of administration throughout the whole course (21 days), on the outcomes in patients with SAH. To our knowledge, the present study is the first to investigate the association between nimodipine techniques of oral administration with patient outcomes.
- To develop and validate an enantioselective LC-MS/MS nimodipine assay in human plasma. The method is simple and involves one step liquid-liquid extraction using a small sample volume (0.3µl).

- To compare nimodipine systemic exposure in SAH patients who experienced poor outcomes with those who experienced favourable outcomes. *Nimodipine systemic exposure* will be quantified using the area under the concentration-time curve at steady state from 0-4h ($AUC_{0\text{-}4h}$). *Primary outcome* will be modified Rankin Scale (mRS) score at 90 days following SAH onset. In addition, we aimed to identify covariates potentially associated with nimodipine exposure.

1.4 Linkage

The thesis contains three projects that are all part of larger project towards optimization of nimodipine therapy in patients with SAH, a life-threatening neurological illness. First, we aimed to answer the following research question "Is there any association between nimodipine mode of administration (i.e., feeding tube administration and tablet form) and outcomes in patients with SAH?" via a conducting a retrospective chart review (RCR) (**CHAPTER 2**). RCR is a widely utilized research methodology in variety of health care disciplines and provides very valuable information that paves the way for lunching a prospective study. The findings of our RCR suggested that there is a trend of having poor outcome in patients who received nimodipine through enteral feeding tubes after adjusting for confounders. However, in order to determine if the observed poor outcomes are attributed to reduced nimodipine exposure, we developed and validated an enantioselective method to determine nimodipine concentrations in human plasma (**CHAPTER 3**). Then, we utilized the method we developed to conduct a prospective pilot observational study to compare nimodipine systemic exposure in SAH patients who experienced poor outcomes with those who experienced favourable outcomes and to identify covariates potentially associated with nimodipine exposure (**CHAPTER 4**). The findings of the proposed research will facilitate the design of a larger prospective multicenter study to determine whether

nimodipine exposure is an independent predictor of SAH patient outcomes and to determine the impact of various covariates on nimodipine pharmacokinetics.

References

1. Gasparotti R, Liserre R. Intracranial aneurysms. Eur Radiol. 2005;15(3):441-7.
2. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365-72.
3. . !!! INVALID CITATION !!! (3).
4. Huang YH, Liao CC, Yang KY. Demographics and Short-Term Outcomes of Spontaneous Subarachnoid Hemorrhage in Young Adults. World Neurosurg. 2017;102:414-9.
5. Ogungbo B, Gregson B, Blackburn A, Barnes J, Vivar R, Sengupta R, et al. Aneurysmal subarachnoid hemorrhage in young adults. J Neurosurg. 2003;98(1):43-9.
6. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012;43(6):1711-37.
7. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354(4):387-96.
8. Diringer MN, Bleck TP, Claude Hemphill J, 3rd, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15(2):211-40.
9. Roos YB, Dijkgraaf MG, Albrecht KW, Beenen LF, Groen RJ, de Haan RJ, et al. Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. Stroke. 2002;33(6):1595-9.
10. Marcolini E, Hine J. Approach to the Diagnosis and Management of Subarachnoid Hemorrhage. West J Emerg Med. 2019;20(2):203-11.
11. Jakubowski J, Kendall B. Coincidental aneurysms with tumours of pituitary origin. J Neurol Neurosurg Psychiatry. 1978;41(11):972-9.
12. Brown RD, Jr., Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. Lancet Neurol. 2014;13(4):393-404.
13. Williams LN, Brown RD, Jr. Management of unruptured intracranial aneurysms. Neurol Clin Pract. 2013;3(2):99-108.
14. Bor AS, Koffijberg H, Wermer MJ, Rinkel GJ. Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis. Neurology. 2010;74(21):1671-9.
15. Broderick JP, Brown RD, Jr., Sauerbeck L, Hornung R, Huston J, 3rd, Woo D, et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. Stroke. 2009;40(6):1952-7.
16. Schievink WI, Michels VV, Piepgras DG. Neurovascular manifestations of heritable connective tissue disorders. A review. Stroke. 1994;25(4):889-903.
17. Broderick JP, Viscoli CM, Brott T, Kernan WN, Brass LM, Feldmann E, et al. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. Stroke. 2003;34(6):1375-81.
18. Broderick JP, Brott T, Tomsick T, Huster G, Miller R. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. N Engl J Med. 1992;326(11):733-6.

19. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke. 2005;36(12):2773-80.
20. Edlow JA, Panagos PD, Godwin SA, Thomas TL, Decker WW, American College of Emergency P, et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. Ann Emerg Med. 2008;52(4):407-36.
21. Bassi P, Bandera R, Loiero M, Tognoni G, Mangoni A. Warning signs in subarachnoid hemorrhage: a cooperative study. Acta Neurol Scand. 1991;84(4):277-81.
22. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. Cephalalgia. 2003;23(10):935-41.
23. Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. Neurosurg Focus. 2009;26(5):E2.
24. Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103-10.
25. Kowalski RG, Claassen J, Kreiter KT, Bates JE, Ostapkovich ND, Connolly ES, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. Jama. 2004;291(7):866-9.
26. Meurer WJ, Walsh B, Vilke GM, Coyne CJ. Clinical Guidelines for the Emergency Department Evaluation of Subarachnoid Hemorrhage. J Emerg Med. 2016;50(4):696-701.
27. Panczykowski D, Pease M, Zhao Y, Weiner G, Ares W, Crago E, et al. Prophylactic Antiepileptics and Seizure Incidence Following Subarachnoid Hemorrhage: A Propensity Score-Matched Analysis. Stroke. 2016;47(7):1754-60.
28. Sames TA, Storrow AB, Finkelstein JA, Magoon MR. Sensitivity of new-generation computed tomography in subarachnoid hemorrhage. Acad Emerg Med. 1996;3(1):16-20.
29. van der Jagt M, Hasan D, Bijvoet HW, Pieterman H, Dippel DW, Vermeij FH, et al. Validity of prediction of the site of ruptured intracranial aneurysms with CT. Neurology. 1999;52(1):34-9.
30. Agid R, Andersson T, Almqvist H, Willinsky RA, Lee SK, terBrugge KG, et al. Negative CT angiography findings in patients with spontaneous subarachnoid hemorrhage: When is digital subtraction angiography still needed? AJNR Am J Neuroradiol. 2010;31(4):696-705.
31. Sayer D, Bloom B, Fernando K, Jones S, Benton S, Dev S, et al. An Observational Study of 2,248 Patients Presenting With Headache, Suggestive of Subarachnoid Hemorrhage, Who Received Lumbar Punctures Following Normal Computed Tomography of the Head. Acad Emerg Med. 2015;22(11):1267-73.
32. Kuntz KM, Kokmen E, Stevens JC, Miller P, Offord KP, Ho MM. Post-lumbar puncture headaches: experience in 501 consecutive procedures. Neurology. 1992;42(10):1884-7.
33. Fox AJ, Symons SP, Aviv RI. CT angiography is state-of-the-art first vascular imaging for subarachnoid hemorrhage. AJNR Am J Neuroradiol. 2008;29(6):e41-2; author reply e6-7.
34. Prestigiacomo CJ, Sabit A, He W, Jethwa P, Gandhi C, Russin J. Three dimensional CT angiography versus digital subtraction angiography in the detection of intracranial aneurysms in subarachnoid hemorrhage. J Neurointerv Surg. 2010;2(4):385-9.
35. Kershenovich A, Rappaport ZH, Maimon S. Brain computed tomography angiographic scans as the sole diagnostic examination for excluding aneurysms in patients with perimesencephalic subarachnoid hemorrhage. Neurosurgery. 2006;59(4):798-801; discussion -2.

36. Luo Z, Wang D, Sun X, Zhang T, Liu F, Dong D, et al. Comparison of the accuracy of subtraction CT angiography performed on 320-detector row volume CT with conventional CT angiography for diagnosis of intracranial aneurysms. Eur J Radiol. 2012;81(1):118-22.
37. Yeung R, Ahmad T, Aviv RI, de Tilly LN, Fox AJ, Symons SP. Comparison of CTA to DSA in determining the etiology of spontaneous ICH. Can J Neurol Sci. 2009;36(2):176-80.
38. Thaker NG, Turner JD, Cobb WS, Hussain I, Janjua N, He W, et al. Computed tomographic angiography versus digital subtraction angiography for the postoperative detection of residual aneurysms: a single-institution series and meta-analysis. J Neurointerv Surg. 2012;4(3):219-25.
39. Heiserman JE, Dean BL, Hodak JA, Flom RA, Bird CR, Drayer BP, et al. Neurologic complications of cerebral angiography. AJNR Am J Neuroradiol. 1994;15(8):1401-7; discussion 8-11.
40. Cloft HJ, Joseph GJ, Dion JE. Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: a meta-analysis. Stroke. 1999;30(2):317-20.
41. Saboori M, Hekmatnia A, Ghazavi A, Basiratnia R, Omidifar N, Hekmatnia F, et al. The comparative study on diagnostic validity of cerebral aneurysm by computed tomography angiography versus digital subtraction angiography after subarachnoid hemorrhage. J Res Med Sci. 2011;16(8):1020-5.
42. Anderson GB, Steinke DE, Petruk KC, Ashforth R, Findlay JM. Computed tomographic angiography versus digital subtraction angiography for the diagnosis and early treatment of ruptured intracranial aneurysms. Neurosurgery. 1999;45(6):1315-20; discussion 20-2.
43. Howard BM, Hu R, Barrow JW, Barrow DL. Comprehensive review of imaging of intracranial aneurysms and angiographically negative subarachnoid hemorrhage. Neurosurg Focus. 2019;47(6):E20.
44. Mitchell P, Wilkinson ID, Hoggard N, Paley MN, Jellinek DA, Powell T, et al. Detection of subarachnoid haemorrhage with magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2001;70(2):205-11.
45. Ogawa T, Inugami A, Fujita H, Hatazawa J, Shimosegawa E, Noguchi K, et al. MR diagnosis of subacute and chronic subarachnoid hemorrhage: comparison with CT. AJR Am J Roentgenol. 1995;165(5):1257-62.
46. Rigamonti A, Ackery A, Baker AJ. Transcranial Doppler monitoring in subarachnoid hemorrhage: a critical tool in critical care. Can J Anaesth. 2008;55(2):112-23.
47. White H, Venkatesh B. Applications of transcranial Doppler in the ICU: a review. Intensive Care Med. 2006;32(7):981-94.
48. Rosen DS, Macdonald RL. Subarachnoid hemorrhage grading scales: a systematic review. Neurocrit Care. 2005;2(2):110-8.
49. Aulmann C, Steudl WI, Feldmann U. [Validation of the prognostic accuracy of neurosurgical admission scales after rupture of cerebral aneurysms]. Zentralbl Neurochir. 1998;59(3):171-80.
50. Oshiro EM, Walter KA, Piantadosi S, Witham TF, Tamargo RJ. A new subarachnoid hemorrhage grading system based on the Glasgow Coma Scale: a comparison with the Hunt and Hess and World Federation of Neurological Surgeons Scales in a clinical series. Neurosurgery. 1997;41(1):140-7; discussion 7-8.
51. Hunt WE, Kosnik EJ. Timing and perioperative care in intracranial aneurysm surgery. Clin Neurosurg. 1974;21:79-89.

52. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81-4.
53. Fischer J, Mathieson C. The history of the Glasgow Coma Scale: implications for practice. Crit Care Nurs Q. 2001;23(4):52-8.
54. Alvarez M, Nava JM, Rue M, Quintana S. Mortality prediction in head trauma patients: performance of Glasgow Coma Score and general severity systems. Crit Care Med. 1998;26(1):142-8.
55. Gotoh O, Tamura A, Yasui N, Suzuki A, Hadeishi H, Sano K. Glasgow Coma Scale in the prediction of outcome after early aneurysm surgery. Neurosurgery. 1996;39(1):19-24; discussion -5.
56. Ducati A. [The clinical grading of subarachnoid hemorrhage]. Minerva Anestesiol. 1998;64(4):109-12.
57. Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. J Neurosurg. 1988;68(6):985-6.
58. Rosen DS, Macdonald RL. Grading of subarachnoid hemorrhage: modification of the world World Federation of Neurosurgical Societies scale on the basis of data for a large series of patients. Neurosurgery. 2004;54(3):566-75; discussion 75-6.
59. Sano H, Inamasu J, Kato Y, Satoh A, Murayama Y, Diseases WC, et al. Modified world federation of neurosurgical societies subarachnoid hemorrhage grading system. Surg Neurol Int. 2016;7(Suppl 18):S502-3.
60. Smith ML, Abrahams JM, Chandela S, Smith MJ, Hurst RW, Le Roux PD. Subarachnoid hemorrhage on computed tomography scanning and the development of cerebral vasospasm: the Fisher grade revisited. Surg Neurol. 2005;63(3):229-34; discussion 34-5.
61. Reilly C, Amidei C, Tolentino J, Jahromi BS, Macdonald RL. Clot volume and clearance rate as independent predictors of vasospasm after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2004;101(2):255-61.
62. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, Jr., et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21-7; discussion -7.
63. Sherlock M, O'Sullivan E, Agha A, Behan LA, Rawluk D, Brennan P, et al. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. Clin Endocrinol (Oxf). 2006;64(3):250-4.
64. Chandy D, Sy R, Aronow WS, Lee WN, Maguire G, Murali R. Hyponatremia and cerebrovascular spasm in aneurysmal subarachnoid hemorrhage. Neurol India. 2006;54(3):273-5.
65. Qureshi AI, Suri MF, Sung GY, Straw RN, Yahia AM, Saad M, et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery. 2002;50(4):749-55; discussion 55-6.
66. Rahman M, Friedman WA. Hyponatremia in neurosurgical patients: clinical guidelines development. Neurosurgery. 2009;65(5):925-35; discussion 35-6.
67. Marr N, Yu J, Kutsogiannis DJ, Mahmoud SH. Risk of Hyponatremia in Patients with Aneurysmal Subarachnoid Hemorrhage Treated with Exogenous Vasopressin Infusion. Neurocrit Care. 2017;26(2):182-90.
68. Marupudi NI, Mittal S. Diagnosis and Management of Hyponatremia in Patients with Aneurysmal Subarachnoid Hemorrhage. J Clin Med. 2015;4(4):756-67.

69. Sayama T, Inamura T, Matsushima T, Inoha S, Inoue T, Fukui M. High incidence of hyponatremia in patients with ruptured anterior communicating artery aneurysms. Neurol Res. 2000;22(2):151-5.
70. Mount DB. The brain in hyponatremia: both culprit and victim. Semin Nephrol. 2009;29(3):196-215.
71. Hasan D, Wijdicks EF, Vermeulen M. Hyponatremia is associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. Ann Neurol. 1990;27(1):106-8.
72. Kruyt ND, Biessels GJ, de Haan RJ, Vermeulen M, Rinkel GJ, Coert B, et al. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage: a meta-analysis. Stroke. 2009;40(6):e424-30.
73. Kruyt ND, Biessels GJ, DeVries JH, Luitse MJ, Vermeulen M, Rinkel GJ, et al. Hyperglycemia in aneurysmal subarachnoid hemorrhage: a potentially modifiable risk factor for poor outcome. J Cereb Blood Flow Metab. 2010;30(9):1577-87.
74. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2012;43(6):1711-37.
75. Dorhout Mees SM, van Dijk GW, Algra A, Kempink DR, Rinkel GJ. Glucose levels and outcome after subarachnoid hemorrhage. Neurology. 2003;61(8):1132-3.
76. McGirt MJ, Woodworth GF, Ali M, Than KD, Tamargo RJ, Clatterbuck RE. Persistent perioperative hyperglycemia as an independent predictor of poor outcome after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2007;107(6):1080-5.
77. Douds GL, Tadzong B, Agarwal AD, Krishnamurthy S, Lehman EB, Cockroft KM. Influence of Fever and hospital-acquired infection on the incidence of delayed neurological deficit and poor outcome after aneurysmal subarachnoid hemorrhage. Neurol Res Int. 2012;2012:479865.
78. Albrecht RF, 2nd, Wass CT, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. Mayo Clin Proc. 1998;73(7):629-35.
79. Suehiro E, Sadahiro H, Goto H, Oku T, Oka F, Fujiyama Y, et al. Importance of Early Postoperative Body Temperature Management for Treatment of Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis. 2016;25(6):1482-8.
80. Reith J, Jorgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet. 1996;347(8999):422-5.
81. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, Ogilvy CS, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. Neurology. 2001;56(10):1299-304.
82. Dhar R, Diringer MN. The burden of the systemic inflammatory response predicts vasospasm and outcome after subarachnoid hemorrhage. Neurocrit Care. 2008;8(3):404-12.
83. Jane JA, Winn HR, Richardson AE. The natural history of intracranial aneurysms: rebleeding rates during the acute and long term period and implication for surgical management. Clin Neurosurg. 1977;24:176-84.
84. Starke RM, Connolly ES, Jr. Rebleeding after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;15(2):241-6.
85. Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. Stroke. 1994;25(7):1342-7.

86. Ameen AA, Illingworth R. Anti-fibrinolytic treatment in the pre-operative management of subarachnoid haemorrhage caused by ruptured intracranial aneurysm. J Neurol Neurosurg Psychiatry. 1981;44(3):220-6.
87. Tang C, Zhang TS, Zhou LF. Risk factors for rebleeding of aneurysmal subarachnoid hemorrhage: a meta-analysis. PLoS One. 2014;9(6):e99536.
88. Hasan D, Vermeulen M, Wijdicks EF, Hijdra A, van Gijn J. Management problems in acute hydrocephalus after subarachnoid hemorrhage. Stroke. 1989;20(6):747-53.
89. Hasan D, Lindsay KW, Vermeulen M. Treatment of acute hydrocephalus after subarachnoid hemorrhage with serial lumbar puncture. Stroke. 1991;22(2):190-4.
90. McIver JI, Friedman JA, Wijdicks EF, Piepgras DG, Pichelmann MA, Toussaint LG, 3rd, et al. Preoperative ventriculostomy and rebleeding after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002;97(5):1042-4.
91. Hellingman CA, van den Bergh WM, Beijer IS, van Dijk GW, Algra A, van Gijn J, et al. Risk of rebleeding after treatment of acute hydrocephalus in patients with aneurysmal subarachnoid hemorrhage. Stroke. 2007;38(1):96-9.
92. Kassell NF, Torner JC, Haley EC, Jr., Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg. 1990;73(1):18-36.
93. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S, et al. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. Neurol Res. 2009;31(2):151-8.
94. Lee KH, Lukovits T, Friedman JA. "Triple-H" therapy for cerebral vasospasm following subarachnoid hemorrhage. Neurocrit Care. 2006;4(1):68-76.
95. Wilkins RH. Cerebral vasospasm. Crit Rev Neurobiol. 1990;6(1):51-77.
96. Vora YY, Suarez-Almazor M, Steinke DE, Martin ML, Findlay JM. Role of transcranial Doppler monitoring in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery. 1999;44(6):1237-47; discussion 47-8.
97. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands. J Neurol Neurosurg Psychiatry. 2000;68(3):337-41.
98. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, et al. Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? Stroke. 2009;40(6):1963-8.
99. Kitazawa T, Eto M, Woodsome TP, Khalequzzaman M. Phosphorylation of the myosin phosphatase targeting subunit and CPI-17 during Ca2+ sensitization in rabbit smooth muscle. J Physiol. 2003;546(Pt 3):879-89.
100. Laher I, Zhang JH. Protein kinase C and cerebral vasospasm. J Cereb Blood Flow Metab. 2001;21(8):887-906.
101. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 1980;6(1):1-9.
102. Geraghty JR, Testai FD. Delayed Cerebral Ischemia after Subarachnoid Hemorrhage: Beyond Vasospasm and Towards a Multifactorial Pathophysiology. Curr Atheroscler Rep. 2017;19(12):50.
103. Rowland MJ, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. Br J Anaesth. 2012;109(3):315-29.

104. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke. 2010;41(10):2391-5.
105. Dankbaar JW, Rijsdijk M, van der Schaaf IC, Velthuis BK, Wermer MJ, Rinkel GJ. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neuroradiology. 2009;51(12):813-9.
106. Pham M, Johnson A, Bartsch AJ, Lindner C, Mullges W, Roosen K, et al. CT perfusion predicts secondary cerebral infarction after aneurysmal subarachnoid hemorrhage. Neurology. 2007;69(8):762-5.
107. Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S, et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. Stroke. 2008;39(11):3015-21.
108. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol. 2011;10(7):618-25.
109. Hart MN. Morphometry of brain parenchymal vessels following subarachnoid hemorrhage. Stroke. 1980;11(6):653-5.
110. Herz DA, Baez S, Shulman K. Pial microcirculation in subarachnoid hemorrhage. Stroke. 1975;6(4):417-24.
111. Koide M, Bonev AD, Nelson MT, Wellman GC. Subarachnoid blood converts neurally evoked vasodilation to vasoconstriction in rat brain cortex. Acta Neurochir Suppl. 2013;115:167-71.
112. Koide M, Bonev AD, Nelson MT, Wellman GC. Inversion of neurovascular coupling by subarachnoid blood depends on large-conductance Ca2+-activated K+ (BK) channels. Proc Natl Acad Sci U S A. 2012;109(21):E1387-95.
113. Wellman GC, Koide M. Impact of subarachnoid hemorrhage on parenchymal arteriolar function. Acta Neurochir Suppl. 2013;115:173-7.
114. Sehba FA, Friedrich V. Cerebral microvasculature is an early target of subarachnoid hemorrhage. Acta Neurochir Suppl. 2013;115:199-205.
115. Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A. Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. Neurochem Res. 1997;22(10):1249-55.
116. Frijns CJ, Fijnheer R, Algra A, van Mourik JA, van Gijn J, Rinkel GJ. Early circulating levels of endothelial cell activation markers in aneurysmal subarachnoid haemorrhage: associations with cerebral ischaemic events and outcome. J Neurol Neurosurg Psychiatry. 2006;77(1):77-83.
117. Budohoski KP, Guilfoyle M, Helmy A, Huuskonen T, Czosnyka M, Kirollos R, et al. The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2014;85(12):1343-53.
118. Vergouwen MD, Vermeulen M, Coert BA, Stroes ES, Roos YB. Microthrombosis after aneurysmal subarachnoid hemorrhage: an additional explanation for delayed cerebral ischemia. J Cereb Blood Flow Metab. 2008;28(11):1761-70.

119. Romano JG, Forteza AM, Concha M, Koch S, Heros RC, Morcos JJ, et al. Detection of microemboli by transcranial Doppler ultrasonography in aneurysmal subarachnoid hemorrhage. Neurosurgery. 2002;50(5):1026-30; discussion 30-1.
120. Giller CA, Giller AM, Landreneau F. Detection of emboli after surgery for intracerebral aneurysms. Neurosurgery. 1998;42(3):490-3; discussion 3-4.
121. Ikeda K, Asakura H, Futami K, Yamashita J. Coagulative and fibrinolytic activation in cerebrospinal fluid and plasma after subarachnoid hemorrhage. Neurosurgery. 1997;41(2):344-9; discussion 9-50.
122. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schutt S, et al. Inflammatory cytokines in subarachnoid haemorrhage: association with abnormal blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry. 2001;70(4):534-7.
123. Naredi S, Lambert G, Friberg P, Zall S, Eden E, Rydenhag B, et al. Sympathetic activation and inflammatory response in patients with subarachnoid haemorrhage. Intensive Care Med. 2006;32(12):1955-61.
124. Lee SJ, Benveniste EN. Adhesion molecule expression and regulation on cells of the central nervous system. J Neuroimmunol. 1999;98(2):77-88.
125. Sozen T, Tsuchiyama R, Hasegawa Y, Suzuki H, Jadhav V, Nishizawa S, et al. Role of interleukin-1beta in early brain injury after subarachnoid hemorrhage in mice. Stroke. 2009;40(7):2519-25.
126. Yamashita T, Abe K. Therapeutic approaches to vascular protection in ischemic stroke. Acta Med Okayama. 2011;65(4):219-23.
127. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. World Neurosurg. 2010;73(1):22-41.
128. Kubota T, Handa Y, Tsuchida A, Kaneko M, Kobayashi H, Kubota T. The kinetics of lymphocyte subsets and macrophages in subarachnoid space after subarachnoid hemorrhage in rats. Stroke. 1993;24(12):1993-2000; discussion -1.
129. Provencio JJ, Fu X, Siu A, Rasmussen PA, Hazen SL, Ransohoff RM. CSF neutrophils are implicated in the development of vasospasm in subarachnoid hemorrhage. Neurocrit Care. 2010;12(2):244-51.
130. Magnoni S, Stocchetti N, Colombo G, Carlin A, Colombo A, Lipton JM, et al. Alpha-melanocyte-stimulating hormone is decreased in plasma of patients with acute brain injury. J Neurotrauma. 2003;20(3):251-60.
131. Mathiesen T, Edner G, Ulfarsson E, Andersson B. Cerebrospinal fluid interleukin-1 receptor antagonist and tumor necrosis factor-alpha following subarachnoid hemorrhage. J Neurosurg. 1997;87(2):215-20.
132. Nakahara T, Tsuruta R, Kaneko T, Yamashita S, Fujita M, Kasaoka S, et al. High-Mobility Group Box 1 Protein in CSF of Patients with Subarachnoid Hemorrhage. Neurocritical Care. 2009;11(3):362.
133. Simard JM, Geng Z, Woo SK, Ivanova S, Tosun C, Melnichenko L, et al. Glibenclamide reduces inflammation, vasogenic edema, and caspase-3 activation after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2009;29(2):317-30.
134. Prunell GF, Svendgaard NA, Alkass K, Mathiesen T. Inflammation in the brain after experimental subarachnoid hemorrhage. Neurosurgery. 2005;56(5):1082-92; discussion -92.

135. Chou SH, Feske SK, Atherton J, Konigsberg RG, De Jager PL, Du R, et al. Early elevation of serum tumor necrosis factor-alpha is associated with poor outcome in subarachnoid hemorrhage. J Investig Med. 2012;60(7):1054-8.
136. Mathiesen T, Andersson B, Loftenius A, von Holst H. Increased interleukin-6 levels in cerebrospinal fluid following subarachnoid hemorrhage. J Neurosurg. 1993;78(4):562-7.
137. Fassbender K, Ries S, Schminke U, Schneider S, Hennerici M. Inflammatory cytokines in CSF in bacterial meningitis: association with altered blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry. 1996;61(1):57-61.
138. Ortega-Gutierrez S, Thomas J, Reccius A, Agarwal S, Lantigua H, Li M, et al. Effectiveness and safety of nicardipine and labetalol infusion for blood pressure management in patients with intracerebral and subarachnoid hemorrhage. Neurocrit Care. 2013;18(1):13-9.
139. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet. 2002;360(9342):1267-74.
140. Spetzler RF, McDougall CG, Albuquerque FC, Zabramski JM, Hills NK, Partovi S, et al. The Barrow Ruptured Aneurysm Trial: 3-year results. J Neurosurg. 2013;119(1):146-57.
141. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366(9488):809-17.
142. Boogaarts HD, van Amerongen MJ, de Vries J, Westert GP, Verbeek AL, Grotenhuis JA, et al. Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Neurosurg. 2014;120(3):605-11.
143. Pare L, Delfino R, Leblanc R. The relationship of ventricular drainage to aneurysmal rebleeding. J Neurosurg. 1992;76(3):422-7.
144. Gruber A, Reinprecht A, Bavinzski G, Czech T, Richling B. Chronic shunt-dependent hydrocephalus after early surgical and early endovascular treatment of ruptured intracranial aneurysms. Neurosurgery. 1999;44(3):503-9; discussion 9-12.
145. Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP. Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. Neurosurgery. 1982;11(3):337-43.
146. Awad IA, Carter LP, Spetzler RF, Medina M, Williams FC, Jr. Clinical vasospasm after subarachnoid hemorrhage: response to hypervolemic hemodilution and arterial hypertension. Stroke. 1987;18(2):365-72.
147. Friedman JA, Pichelmann MA, Piepgras DG, McIver JI, Toussaint LG, 3rd, McClelland RL, et al. Pulmonary complications of aneurysmal subarachnoid hemorrhage. Neurosurgery. 2003;52(5):1025-31; discussion 31-2.
148. Lopez-Arrieta JM, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. Cochrane Database Syst Rev. 2002(3):Cd000147.
149. Wessell A, Kole MJ, Badjatia N, Parikh G, Albrecht JS, Schreibman DL, et al. High Compliance with Scheduled Nimodipine Is Associated with Better Outcome in Aneurysmal Subarachnoid Hemorrhage Patients Cotreated with Heparin Infusion. Front Neurol. 2017;8:268.

150. Tomassoni D, Lanari A, Silvestrelli G, Traini E, Amenta F. Nimodipine and its use in cerebrovascular disease: evidence from recent preclinical and controlled clinical studies. Clin Exp Hypertens. 2008;30(8):744-66.
151. Scriabine A, van den Kerckhoff W. Pharmacology of nimodipine. A review. Ann N Y Acad Sci. 1988;522:698-706.
152. Auer LM, Oberbauer RW, Schalk HV. Human pial vascular reactions to intravenous Nimodipine-infusion during EC-IC bypass surgery. Stroke. 1983;14(2):210-3.
153. Keyrouz SG, Diringer MN. Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage. Crit Care. 2007;11(4):220.
154. Liu Y-f, Qiu H-C, Su J, Jiang W-J. Drug treatment of cerebral vasospasm after subarachnoid hemorrhage following aneurysms. Chinese Neurosurgical Journal. 2016;2(1):4.
155. Varsos VG, Liszczak TM, Han DH, Kistler JP, Vielma J, Black PM, et al. Delayed cerebral vasospasm is not reversible by aminophylline, nifedipine, or papaverine in a "two-hemorrhage" canine model. J Neurosurg. 1983;58(1):11-7.
156. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg. 1988;68(4):505-17.
157. Philippon J, Grob R, Dagreou F, Guggiari M, Rivierez M, Viars P. Acta Neurochir (Wien) (1986) 82:110-114 eCt ahirurgica Prevention of Vasospasm in Subarachnoid Haemorrhage. A Controlled Study with Nimodipine. 1986:110-4.
158. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989;298(6674):636-42.
159. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, et al. Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308(11):619-24.
160. Allen GS, Bahr AL. Cerebral arterial spasm: part 10. Reversal of acute and chronic spasm in dogs with orally administered nifedipine. Neurosurgery. 1979;4(1):43-7.
161. Allen GS, Banghart SB. Cerebral arterial spasm: part 9. In vitro effects of nifedipine on serotonin-, phenylephrine-, and potassium-induced contractions of canine basilar and femoral arteries. Neurosurgery. 1979;4(1):37-42.
162. Scr A, Bat R, Kazda S, Towart R, Schluter T, Ramsch K-d, et al. Nimodipine. 1985;3(28).
163. Solubility enhancement of nimodipine through preparation of Soluplus® dispersions. Journal of Applied Pharmaceutical Science. 2019;9(9):30-7.
164. Ms L, Em S. Nimodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs. 1989;37(5):669-99.
165. Towart R, Wehinger E, Meyer H, Kazda S. The effects of nimodipine, its optical isomers and metabolites on isolated vascular smooth muscle. Arzneimittelforschung. 1982;32(4):338-46.
166. <BSC CLASSIFICATION.pdf>.
167. Uchida S, Yamada S, Nagai K, Deguchi Y, Kimura R. Brain pharmacokinetics and in vivo receptor binding of 1,4-dihydropyridine calcium channel antagonists. Life Sci. 1997;61(21):2083-90.
168. Kazda S, Garthoff B, Krause HP, Schlossmann K. Cerebrovascular effects of the calcium antagonistic dihydropyridine derivative nimodipine in animal experiments. Arzneimittelforschung. 1982;32(4):331-8.

169. R.Towart EW, H.Meyer, and S.Kazda. The Effect of Nimodipine, its Optical Isomers and Metabolites on Isolated Vascular Smooth Muscle. ArzneimForsch/Drug Res. 1982;32(1):338-46.
170. Li RW, Tse CM, Man RY, Vanhoutte PM, Leung GP. Inhibition of human equilibrative nucleoside transporters by dihydropyridine-type calcium channel antagonists. Eur J Pharmacol. 2007;568(1-3):75-82.
171. Blardi P, Urso R, De Lalla A, Volpi L, Perri TD, Auteri A. Nimodipine: drug pharmacokinetics and plasma adenosine levels in patients affected by cerebral ischemia. Clin Pharmacol Ther. 2002;72(5):556-61.
172. Rudolphi KA, Schubert P, Parkinson FE, Fredholm BB. Neuroprotective role of adenosine in cerebral ischaemia. Trends Pharmacol Sci. 1992;13(12):439-45.
173. Sweeney MI. Neuroprotective effects of adenosine in cerebral ischemia: window of opportunity. Neurosci Biobehav Rev. 1997;21(2):207-17.
174. Langley MS, Sorkin EM. Nimodipine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs. 1989;37(5):669-99.
175. Muck W, Ahr G, Kuhlmann J. Nimodipine. Potential for drug-drug interactions in the elderly. Drugs & aging. 1995;6(3):229-42.
176. Ltd BA. PRODUCT INFORMATION NIMOTOP®. 2017.
177. Donald K. Woodward PD, Jimmi Hatton, Pharm.D., FCCP,, Mary H. H. Ensom PD, FCCP, Byron Young, M.D., Robert Dempsey, M.D., and, G. Dennis Clifton PD, FCCP. al-Acid Glycoprotein Concentrations and Cerebrospinal Fluid Drug Distribution after Subarachnoid Hemorrhage. Pharmacotherapy 1998;18(5):1062-68.
178. Adam P, Sobek O, Táborský L, Hildebrand T, Tutterová O, Zácek P. CSF and serum orosomucoid (alpha-1-acid glycoprotein) in patients with multiple sclerosis: a comparison among particular subgroups of MS patients. Clin Chim Acta. 2003;334(1-2):107-10.
179. Ha HR, Pletscher W, Leuenberger PM, Sticher O, Meier PJ. Measurement of Nimodipine Metabolism in Rat Liver Microsomes by High-Performance Liquid Chromatography. Journal of Liquid Chromatography. 2007;18(11):2243-55.
180. Scherling D, Bühner K, Krause HP, Karl W, Wünsche C. Biotransformation of nimodipine in rat, dog, and monkey. Arzneimittel-Forschung. 1991;41(4):392-8.
181. Rämsch KD, Ahr G, Tettenborn D, Auer LM. Overview on pharmacokinetics of nimodipine in healthy volunteers and in patients with subarachnoid hemorrhage. Neurochirurgia. 1985;28 Suppl 1:74-8.
182. Anonymous. Population pharmacokinetic analysis for nimodipine. Japanese Journal of Clinical Pharmacology and Therapeutics. 1999;30(1):229-30.
183. Becker C, Hilgert D, Platt D, Krauss D, Spahn H, Mutschler E. Pharmacokinetics of nimodipine and its major metabolites in elderly patients with cerebral disorders. European Journal of Pharmacology. 1990;183(6):2298.
184. Fischer C, Schonberger F, Muck W, Heuck K, Eichelbaum M. Simultaneous assessment of the intravenous and oral disposition of the enantiomers of racemic nimodipine by chiral stationary-phase high-performance liquid chromatography and gas chromatography/mass spectroscopy combined with a stable isotope technique. J Pharm Sci. 1993;82(3):244-50.
185. Michelson G, Wärntges S, Leidig S, Lötsch J, Geisslinger G. Nimodipine plasma concentration and retinal blood flow in healthy subjects. Investigative Ophthalmology & Visual Science. 2006;47(8):3479-86.

186. Muck W, Heine PR, Breuel HP, Niklaus H, Horkulak J, Ahr G. The effect of multiple oral dosing of nimodipine on glibenclamide pharmacodynamics and pharmacokinetics in elderly patients with type-2 diabetes mellitus. International Journal of Clinical Pharmacology and Therapeutics. 1995;33(2):89-94.
187. Wanner-Olsen H, Gaarskaer FB, Mikkelsen EO, Jakobsen P, Voldby B. Studies on concentration-time profiles of nimodipine enantiomers following intravenous and oral administration of nimodipine in patients with subarachnoid hemorrhage. Chirality. 2000;12(9):660-4.
188. Zisaki A, Miskovic L, Hatzimanikatis V. Antihypertensive drugs metabolism: an update to pharmacokinetic profiles and computational approaches. Curr Pharm Des. 2015;21(6):806-22.
189. Rämsch KD, Graefe KH, Scherling D, Sommer J, Ziegler R. Pharmacokinetics and metabolism of calcium-blocking agents nifedipine, nitrendipine, and nimodipine. Am J Nephrol. 1986;6 Suppl 1:73-80.
190. Abboud T, Andresen H, Koeppen J, Czorlich P, Duehrsen L, Stenzig J, et al. Serum levels of nimodipine in enteral and parenteral administration in patients with aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien). 2015;157(5):763-7.
191. Carcas AJ, Abad-Santos F, De Rosendo JM, Frias J. Nimodipine transfer into human breast milk and cerebrospinal fluid. Annals of Pharmacotherapy. 1996;30(2):148-50.
192. Hynynen M, Siltanen T, Sahlman A, Pohjasvaara T, Muck W, Kaste M. Continuous infusion of nimodipine during coronary artery surgery: Haemodynamic and pharmacokinetic study. British Journal of Anaesthesia. 1995;74(5):526-33.
193. Jakobsen P, Mikkelsen EO, Laursen J, Jensen F. Determination of nimodipine by gas chromatography using electron-capture detection; External factors influencing nimodipine concentrations during intravenous administration. Journal of Chromatography - Biomedical Applications. 1986;374(2):383-7.
194. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European Journal of Clinical Pharmacology. 1993;45(4):363-6.
195. Ramsch KD, Graefe KH, Scherling D. Pharmacokinetics and metabolism of calcium-blocking agents nifedipine, nitrendipine, and nimodipine. American Journal of Nephrology. 1986;6(SUPPL. 1):73-80.
196. Scheller C, Vogel AS, Simmermacher S, Rachinger JC, Prell J, Strauss C, et al. Prophylactic intravenous nimodipine treatment in skull base surgery: pharmacokinetic aspects. Journal Of Neurological Surgery Part A, Central European Neurosurgery. 2012;73(3):153-9.
197. Scheller C, Wienke A, Wurm F, Vogel AS, Simmermacher S, Prell J, et al. Enteral or parenteral nimodipine treatment: A comparative pharmacokinetic study. Journal of Neurological Surgery, Part A: Central European Neurosurgery. 2014;75(2):84-90.
198. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage – a pilot study. European Journal of Clinical Pharmacology. 2007;63:355-61.
199. Steudel WI, Carvi M, Lorenz R. Prognostic significance of the concentration of nimodipine in the CSF and plasma in acute subarachnoid hemorrhage. New Trends in Clinical Neuropharmacology. 1989;3(2):100.
200. Vinge E, Andersson KE, Brandt L. Pharmacokinetics of nimodipine in patients with aneurysmal subarachnoid haemorrhage. European Journal of Clinical Pharmacology. 1986;30(4):421-5.

201. Sramek JJ, Heller AH, Sundaresan PR, Lettieri J, Sawin S, Cutler NR. Safety and tolerance of intravenous nimodipine. Ann Pharmacother. 1994;28(10):1143-8.
202. Fleishaker JC, Hulst LK, Peters GR. Lack of a pharmacokinetic/pharmacodynamic interaction between nimodipine and tirilazad mesylate in healthy volunteers. Journal Of Clinical Pharmacology. 1994;34(8):837-41.
203. Gengo FM, Fagan SC, Krol G, Bernhard H. Nimodipine disposition and haemodynamic effects in patients with cirrhosis and age-matched controls. British Journal of Clinical Pharmacology. 1987;23(1):47-53.
204. Gualano V, Ntsikoussalabongui B, Mignot A, Duvauchelle T, Felices M, Guillaume M, et al. Comparative bioavailability of two oral nimodipine formulations after administration to 24 healthy volunteers. Clinical Drug Investigation. 1999;17(6):475-82.
205. He Z, Zhong D, Chen X, Liu X, Tang X, Zhao L. Development of a dissolution medium for nimodipine tablets based on bioavailability evaluation. European Journal Of Pharmaceutical Sciences: Official Journal Of The European Federation For Pharmaceutical Sciences. 2004;21(4):487-91.
206. Liu XD, Xie L, Xu GQ, Wang J, Zhou YC, Liu GQ. Variability of nimodipine pharmacokinetics in healthy Chinese males. Chinese Journal of Pharmacology and Toxicology. 1996;10(1):25-7.
207. Muck W, Tanaka T, Ahr G, Kuhlmann J. No interethnic differences in stereoselective disposition of oral nimodipine between Caucasian and Japanese subjects. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(4):163-71.
208. Qin F, Ma Y, Wang Y, Chen L, Wang D, Li F. Determination of nimodipine in human plasma by ultra performance liquid chromatography-tandem mass spectrometry and pharmacokinetic application. Journal of Pharmaceutical and Biomedical Analysis. 2008;46(3):557-62.
209. Qiu F, Chen X, Li X, Zhong D. Determination of nimodipine in human plasma by a sensitive and selective liquid chromatography-tandem mass spectrometry method. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences. 2004;802(2):291-7.
210. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, et al. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. British Journal Of Clinical Pharmacology. 1991;32(3):335-40.
211. Zhao Y, Zhai D, Chen X, Yu Q, He H, Sun Y, et al. Determination of nimodipine in human plasma by HPLC-ESI-MS and its application to a bioequivalence study. Journal of Chromatographic Science. 2010;48(2):81-5.
212. 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. European Journal Of Clinical Pharmacology. 2009;65(6):579-84.
213. Breuel HP, Muck W, Heine PR, Schmage N, Niklaus H, Kuhlmann J. The influence of nimodipine on hemodynamic parameters and peak and trough plasma concentrations of nifedipine chronically administered to elderly hypertensive patients. International Journal of Clinical Pharmacology and Therapeutics. 1995;33(2):109-13.
214. Eicher H, Hilgert D, Zeeh J, Platt D, Becker C, Mutschler E. Pharmacokinetics of nimodipine in multimorbid elderly patients with chronic brain failure. Archives of Gerontology and Geriatrics. 1992;14(3):309-19.

215. Heine PR, Weyer G, Breuel HP, Muck W, Schmage N, Kuhlmann J. Lack of interaction between diazepam and nimodipine during chronic oral administration to healthy elderly subjects. British Journal of Clinical Pharmacology. 1994;38(1):39-43.
216. Hernández-Hernández R, Coll T, Rachitzky P, Armas-Hernández MJ, Armas-Padilla MC, Velasco M, et al. Comparison of two nimodipine formulations in healthy volunteers. Journal Of Human Hypertension. 2002;16 Suppl 1:S142-S4.
217. Kirch W, Ramsch KD, Duhrsen U, Ohnhaus EE. Clinical pharmacokinetics of nimodipine in normal and impaired renal function. International Journal of Clinical Pharmacology Research. 1984;4(5):381-4.
218. Muck W, Breuel HP, Kuhlmann J. The influence of age on the pharmacokinetics of nimodipine. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(7):293-8.
219. Muck W, Heine PR, Schmage N, Niklaus H, Horkulak J, Breuel HP. Steady-state pharmacokinetics of nimodipine during chronic administration of indometacin in elderly healthy volunteers. Arzneimittel-Forschung/Drug Research. 1995;45(4):460-2.
220. Mück W, Wingender W, Seiberling M, Woelke E, Rämsch KD, Kuhlmann J. Influence of the H2-receptor antagonists cimetidine and ranitidine on the pharmacokinetics of nimodipine in healthy volunteers. European Journal Of Clinical Pharmacology. 1992;42(3):325-8.
221. Terziivanov D, Atanasova I, Dimitrova V, Robeva R, Unger S, Muck W. Pharmacokinetic variability of nimodipine disposition after single and multiple oral dosing to hypertensive renal failure patients: Parametric and nonparametric population analysis. International Journal of Clinical Pharmacology and Therapeutics. 1999;37(8):404-12.
222. W.Muck HPB, J.Kuhlmann. The influence of age on pharmacokinetics of nimodipine*. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(7):293-8.
223. Eicher H, Hilgert D, Zeeh J, Platt D, Becker C, Mutschler E. Pharmacokinetics of nimodipine in multimorbid elderly patients with chronic brain failure. Arch Gerontol Geriatr. 1992;14(3):309-19.
224. Vinge E, Andersson KE, Brandt L, Ljunggren B, Nilsson LG, Rosendal-Helgesen S. Pharmacokinetics of nimodipine in patients with aneurysmal subarachnoid haemorrhage. European Journal Of Clinical Pharmacology. 1986;30(4):421-5.
225. Albanna W, Weiss M, Conzen C, Clusmann H, Schneider T, Reinsch M, et al. Systemic and Cerebral Concentration of Nimodipine During Established and Experimental Vasospasm Treatment. World Neurosurg. 2017.
226. Kirch W, Rämsch KD, Dührsen U, Ohnhaus EE. Clinical pharmacokinetics of nimodipine in normal and impaired renal function. International Journal Of Clinical Pharmacology Research. 1984;4(5):381-4.
227. Terziivanov D, Atanasova I, Dimitrova V, Robeva R, Unger S, Mück W. Pharmacokinetic variability of nimodipine disposition after single and multiple oral dosing to hypertensive renal failure patients: parametric and nonparametric population analysis. International Journal Of Clinical Pharmacology And Therapeutics. 1999;37(8):404-12.
228. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, et al. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. British Journal of Clinical Pharmacology. 1991;32(3):335-40.
229. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage - a pilot study. European Journal Of Clinical Pharmacology. 2007;63(4):355-61.

230. Fuhr U, Maier-Brüggemann A, Blume H, Mück W, Unger S, Kuhlmann J, et al. Grapefruit juice increases oral nimodipine bioavailability. International Journal Of Clinical Pharmacology And Therapeutics. 1998;36(3):126-32.
231. Heine PR, Weyer G, Breuel HP, Mück W, Schmage N, Kuhlmann J. Lack of interaction between diazepam and nimodipine during chronic oral administration to healthy elderly subjects. British Journal Of Clinical Pharmacology. 1994;38(1):39-43.
232. Breuel HP, Heine PR, Mück W, Niklaus H, Schmage N, Kuhlmann J. Chronic administration of nimodipine and propranolol in elderly normotensive subjects--an interaction study. International Journal Of Clinical Pharmacology And Therapeutics. 1995;33(2):103-8.
233. Bruderer S, Zisowsky J, Fuseau E, Gutierez M, Dingemanse J. Investigation of pharmacokinetic and pharmacodynamic interactions between clazosentan and nimodipine in asah patients: A population analysis. Basic and Clinical Pharmacology and Toxicology. 2011;109:150.
234. Nimotop(monograph).Mississauga, Ontario: Bayer Inc; 2014.12.
235. Abboud T, Regelsberger J. Serum Levels of Nimodipine in Enteral and Parenteral Administration in Patients with Aneurysmal Subarachnoid Hemorrhage. Acta Neurochir (Wien). 2015;157(7):1133-4.
236. Schmith VD, Foss JF. Effects of inflammation on pharmacokinetics/pharmacodynamics: increasing recognition of its contribution to variability in response. Clin Pharmacol Ther. 2008;83(6):809-11.
237. 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):238-42.
238. Riva R, Pegoli M, Contin M, Perrone A, Mohamed S, Zanello M. Cerebrospinal Fluid Concentrations of Nimodipine Correlate With Long-term Outcome in Aneurysmal Subarachnoid Hemorrhage: Pilot Study. Clin Neuropharmacol. 2019.
239. Soppi V, Karamanakos PN, Koivisto T, Kurki MI, Vanninen R, Jaaskelainen JE, et al. A randomized outcome study of enteral versus intravenous nimodipine in 171 patients after acute aneurysmal subarachnoid hemorrhage. World Neurosurg. 2012;78(1-2):101-9.
240. Kronvall E, Undren P, Romner B, Saveland H, Cronqvist M, Nilsson OG. Nimodipine in aneurysmal subarachnoid hemorrhage: a randomized study of intravenous or peroral administration. J Neurosurg. 2009;110(1):58-63.
241. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European journal of clinical pharmacology. 1993;45(4):363-6.
242. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. Eur J Clin Pharmacol. 1993;45(4):363-6.
243. Fischer C, Schönberger F, Mück W, Heuck K, Eichelbaum M. Simultaneous assessment of the intravenous and oral disposition of the enantiomers of racemic nimodipine by chiral stationary-phase high-performance liquid chromatography and gas chromatography/mass spectroscopy combined with a stable isotope technique. J Pharm Sci. 1993;82(3):244-50.
244. Wanner-Olsen H, Gaarskær FB, Mikkelsen EO, Jakobsen P, Voldby B. Studies on concentration-time profiles of nimodipine enantiomers following intravenous and oral administration of nimodipine in patients with subarachnoid hemorrhage. Chirality. 2000;12(9):660-4.

245. Muck WM. Enantiospecific determination of nimodipine in human plasma by liquid chromatography-tandem mass spectrometry. Journal of Chromatography A. 1995;712(1):45-53.

Chapter 2 The Impact of Nimodipine Administration through Feeding Tube on Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage

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Keywords: nimodipine; subarachnoid hemorrhage; feeding tube; delayed cerebral ischemia; vasospasm; enteral administration

2.1 Abstract

PURPOSE: Delayed cerebral ischemia (DCI) and vasospasm are the main challenges contributing to unfavorable outcomes following aneurysmal subarachnoid hemorrhage. Nimodipine has been shown to decrease the incidence of delayed cerebral ischemia and improve outcomes. In patients who are unable to swallow, nimodipine tablets are crushed and administered through enteral feeding tubes. However, it is not clear whether this may result in reduced clinical effectiveness. The aims of the study were to investigate the impact of nimodipine administration through enteral feeding tubes, in the first 7 days and over the 21-days period on patient outcomes. **METHODS:** A retrospective chart review of subarachnoid hemorrhage patients admitted at the University of Alberta Hospital, Edmonton, Alberta, Canada was carried out. Logistic regression modelling was utilized to identify predictors of vasospasm and delayed cerebral ischemia. Main outcome measures were angiographic evidence of moderate to severe vasospasm, development of delayed cerebral ischemia and hospital mortality. **RESULTS:** 85 patients were included. Following adjustment for disease severity, nimodipine administration technique was associated with vasospasm in the first 7 days of patient admission where patients receiving nimodipine via enteral feeding tubes had increased odds of vasospasm compared to those administered it as whole tablets (OR 8.9, 95% CI 1.1-73.1, *p* value 0.042). When analyzed over the 21-day period, nimodipine administration by feeding tube was associated with increased odds of DCI compared to whole tablets (OR 38.1, 95% CI 1.4-1067.9, *p* value 0.032). **CONCLUSIONS:** Our findings suggest that nimodipine administration via enteral feeding tubes may be associated with vasospasm and DCI in subarachnoid hemorrhage patients secondary to reduced exposure. Prospective studies are needed to confirm such association and alternate methods of administration should be explored to ensure patients are getting the benefits of nimodipine.

2.2 Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a life-threatening condition characterized by the extravasation of blood into the subarachnoid space secondary to a ruptured intracranial aneurysm. Although SAH accounts for 5-10% of all strokes, it affects patients at a relatively young age leading to premature loss of productive life. Mortality rates secondary to SAH has been reported to range from 30-50%, leaving the rest of patients with different degrees of disability (6-8). Although there are various medical and neurological complications following SAH, delayed cerebral ischemia (DCI) and vasospasm are the main challenges that contribute to unfavorable patient outcomes. Effective prevention of DCI can significantly improve the functional outcomes of patients (98, 246). The role of nimodipine, a dihydropyridine calcium channel blocker with selectivity towards the cerebral blood vessels, in preventing DCI has been investigated by several randomized clinical trials. It has been shown to decrease the incidence of DCI and improve patient outcomes (156-159). Therefore, the current guidelines suggests that all patients who are admitted for SAH to receive nimodipine for 21 days orally and to be started within 96 hours from ictus (74). In our institution, all patients presenting with SAH receive oral nimodipine 60 mg every 4 hours for 21 days. Nimodipine oral tablet is the only available formulation in Canada. Therefore, patients will swallow the whole tablets if they are able to, otherwise, nimodipine tablets are crushed at bedside, suspended in water, and administered immediately through enteral feeding tubes (FT) for those who are unable to swallow, such as those with altered mental status or mechanically ventilated. However, nimodipine drug product monograph states that the tablet should not be crushed as it may result in reduced drug bioavailability (247). In addition, few small studies have reported reduced bioavailability of nimodipine administered through FT and in those with high grade SAH (241, 248). It is not clear, however, whether this technique of administration result in reduced clinical effectiveness and in turn poor outcomes. Although the evidence supporting a

correlation between nimodipine plasma concentrations and patient outcomes is scarce and not clear. In general, poor absorption of drugs leads to variation in clinical response resulted from the alteration plasma exposure (249-251). Therefore, the present study aimed to answer the following research question: Among SAH patients, is taking nimodipine by enteral feeding tube associated with worse outcomes compared to those who swallow nimodipine whole tablets?

The primary aim of the current study was to investigate the impact of nimodipine administration through enteral feeding tubes, in the first 7 days from onset, on the outcomes in patients with SAH. We chose the first 7 days of exposure as the onset of vasospasm and DCI are generally within that time period. In addition, the secondary aim was to determine the impact of nimodipine mode of administration throughout the whole course (21 days), on the outcomes in patients with SAH. To our knowledge, the present study is the first to investigate the association between nimodipine techniques of oral administration with patient outcomes.

2.3 Methods

2.3.1 Study Design

A retrospective chart review of adult patients diagnosed with SAH and admitted to the University of Alberta Hospital, Edmonton, Canada from January 2016 to December 2018. The study was approved by the Health Research Ethics Board (HERB) of the University of Alberta and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

2.3.2 Study Population

Patient medical records (paper and electronic) were requested based on ICD-10-CA codes for SAH. The codes included were: I60.0 Subarachnoid hemorrhage from carotid siphon and bifurcation, I60.1 Subarachnoid hemorrhage from middle cerebral artery, I60.2 Subarachnoid hemorrhage from anterior communicating artery, I60.3 Subarachnoid hemorrhage from posterior communicating artery, I60.4 Subarachnoid hemorrhage from basilar artery, I60.5 Subarachnoid hemorrhage from vertebral artery, I60.6 Subarachnoid hemorrhage from other intracranial arteries, and I60.7 Subarachnoid hemorrhage from intracranial artery, unspecified. The inclusion criteria were adult patients (age ≥ 18 years) admitted to the University of Alberta Hospital Neurosciences intensive care unit (ICU) with aneurysmal subarachnoid hemorrhage diagnosis and were treated with nimodipine regardless of the mode of administration. The exclusion criteria were the following: non-aneurysmal SAH, delayed presentation and those who were treated with nimodipine for less than 4 days.

2.3.3 Data Extraction

Patients' charts were reviewed and data were collected and managed using REDCap database capture tool hosted at the University of Alberta (252). Patients' demographics (age, sex, height, weight, and body mass index (BMI), past medical history (history of diabetes, hypertension, kidney, and liver disease) and social history (smoking and alcohol intake) were recorded. In addition, the following baseline data were included: admission Glasgow coma scale (GCS), World Federation of Neurological Surgeons (WFNS) grade, Fisher scale, Acute Physiology and Chronic Health Evaluation (APACHE II) score, aneurysm location, and aneurysm intervention (surgical clipping, endovascular coiling or other). APACHE II physiological subscore was determined by subtracting admission GCS and age from APACHE II score.

Nimodipine administration record including dose, frequency, duration, method of administration (swallowed whole tablets (PO) vs being crushed and administered by enteral feeding tube (FT)) and any missed doses were recorded. In addition, administration of interacting drugs (cytochrome P450 enzyme inducers and inhibitors) was collected. The median percentage of nimodipine administration was calculated by dividing the number of treatment days by the hospital length of stay in the first week. In addition, for the 21-days full period, the percentage was calculated by dividing the number of days of nimodipine treatment by 21 days or hospital length of stay (if shorter than 21 days). Primary outcomes collected included angiographic evidence of moderate to severe vasospasm (diagnosed through digital subtraction angiography), development of DCI and hospital mortality. DCI was defined as the documentation of new onset focal neurological impairment (such as hemiparesis or aphasia), cerebral infarction or a decrease of at least 2 points in GCS and cannot be explained by other causes (104). In addition, hospital, ICU length of stay, need for external ventricular drain (EVD), re-bleeding, and discharge disposition were recorded.

2.3.4 Data Analysis

Patients' baseline characteristics and the outcomes were summarized. Continuous variables that are normally distributed were presented as mean ± standard deviation and compared by Student's t test; otherwise, they were presented as median with interquartile range (IQR) and compared by Wilcoxon rank sum test. Categorical variables were displayed as frequency and percentage, n (%) and compared by χ^2 or Fisher exact test, as appropriate. For the primary aim, patients who took nimodipine by enteral feeding tubes ≥ 4 days in the first week were classified as feeding tube group (FT7) and for those who were administered nimodipine as whole tablets ≥ 4 days in the first week were classified as oral group (PO7). For the secondary aim, patients who were administered nimodipine as whole tablets ≥50% of the duration of therapy (up to 21-days) were considered as

oral group (PO21). Otherwise, they were included in the feeding tube group (FT21). The association between individual covariates (such as nimodipine administration by feeding tube, baseline characteristics and disease severity) and primary outcomes were determined using univariate logistic regression. Variables with estimated p value of < 0.2 or biologically plausible were included in multivariate logistic regression models and adjusted odds ratios (OR) were determined. The fit of the final model was confirmed by using Hosmer–Lemeshow goodness-of-fit test. Area under the receiver operating characteristic (ROC) curve was determined to confirm model discrimination. Missing data, if any, were handled by complete case analysis. Level of significance was set at p value < 0.05. STATA software version 15 (STATA Corp, College station, Texas) was used for data analysis.

2.4 Results

2.4.1 Study Participants

Medical records of 134 patients were identified. A total of 49 patients were excluded as they did not meet the inclusion criteria (**Figure 2-1**). As a result, 85 patients were included in the present study.

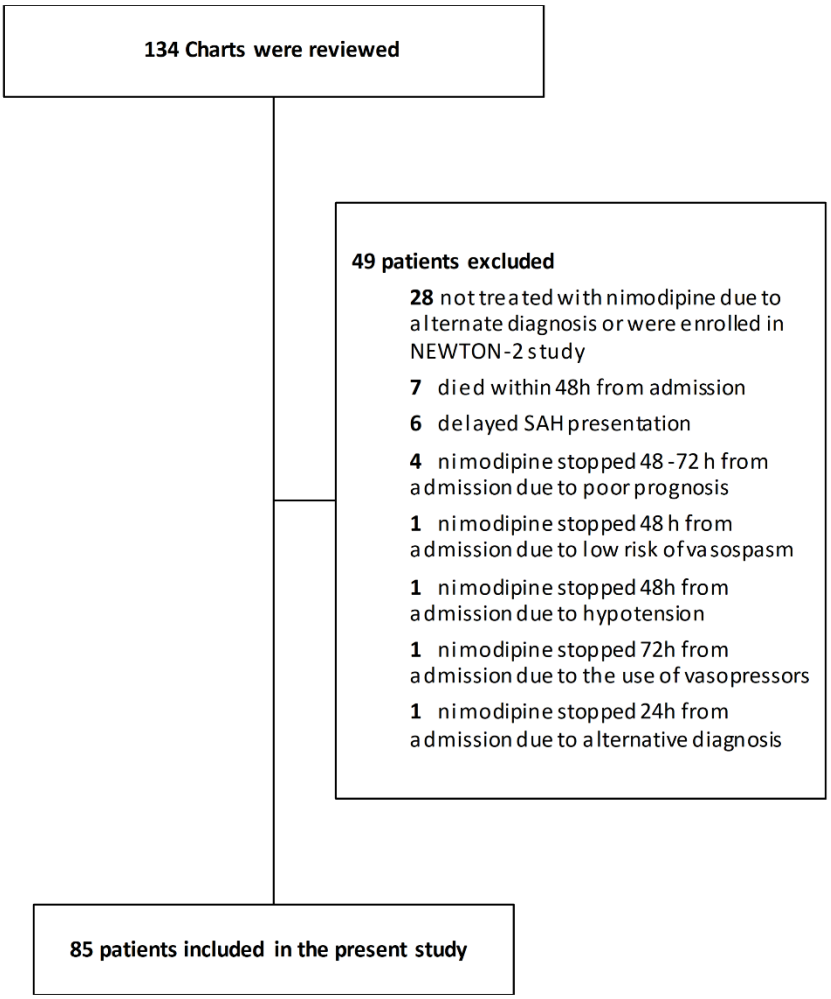

Figure 2-1: Flow chart of patients included in the present study

2.4.2 Baseline Characteristics

Among the 85 included patients, 60 took nimodipine as whole tablets (PO7) and 25 got the drug via feeding tube (FT7) in the first week. Patients' baseline characteristics are presented in **Table 2-1**. Generally, both groups were comparable with regards to their demographics, past medical and social history. The mean ages in the FT7 and PO7 groups were 52 ± 11 and 55 ± 14 years, respectively and approximately two-thirds of the patients were females. On the other hand, as expected, patients in the FT7 group were generally sicker compared to the PO7 group. They had lower GCS on admission [8 (IQR 8) vs 15 (IQR 1), *p* value <0.001], and higher WFNS grade (*p* value <0.001), Fisher Scale (*p* value 0.009) and APACHE II subscore (*p* value 0.0008) compared to PO7 group. Besides, more patients got their aneurysm treated with endovascular coiling in the PO7 group compared to FT7 group (*p* value 0.049). None of the patients included in the current study had history of liver or kidney disease.

Table 2-1: Baseline characteristics of patients included in the study

	PO7 (n=60)	**FT7 (n=25)**	***p* value**
Age, mean ± SD	55 ± 14	52 ± 11	0.387
Female sex, n (%)	40 (67)	14 (56)	0.352
Height (cm), mean ± SD [1]	166 ± 9	172 ± 8	0.015
Weight (kg), mean ± SD	78 ± 20	81 ± 26	0.632
BMI, mean ± SD [1]	28 ± 7	27 ± 8	0.485
BMI categories, n (%)[1]			0.195
17-24.9 kg/m^2	22 (37)	11 (46)	
25-29.9 kg/m^2	19 (32)	10 (42)	
≥30 kg/m^2	19 (32)	3 (13)	
Medical history			
Hypertension, n (%)	23 (38)	5 (20)	0.101
Diabetes, n (%)	7 (12)	3 (12)	1.000
Smoking history, n (%)			
Smoker/Ex-smoker	28 (47)	14 (56)	0.480
Non-smoker	14 (23)	3 (12)	
Unknown	18 (30)	8 (32)	
Alcohol history, n (%)			
Heavy drinker	8 (13)	5 (20)	0.512
Others	52 (87)	20 (80)	
SAH characteristics, n (%)			
Location			0.101
MCA	9 (15)	8 (32)	
ACOMM	30 (50)	6 (24)	
PCOM	7 (12)	5 (20)	
Others	14 (23)	6 (24)	

Intervention			0.049
Coil	42 (70)	11 (44)	
Clip	17 (28)	12 (48)	
Others	1 (2)	2 (8)	
Fisher Scale [2]			0.009
I-II	24 (41)	3 (12)	
III-IV	34 (59)	22 (88)	
WFNS grade			<0.001
Grade I-III	55 (92)	8 (32)	
Grade IV-V	5 (8)	17 (68)	
Admission GCS, median ± IQR	15 ± 1	8 ± 8	<0.001
APACHE, mean ± SD	12 ± 4	20 ± 5	<0.001
APACHE sub score, mean ± SD	8 ± 3	12 ± 5	0.0008
CYP enzyme inducer, n (%)	2 (3)	4 (16)	0.059

ACOMM, anterior communicating artery; APACHE, Acute Physiology and Chronic Healthy Evaluation; BMI, body mass index; CYP, cytochrome P450; FT7, patients who took nimodipine by feeding tube (crushed) in the first week; GCS, Glasgow Coma Scale; MCA, middle cerebral artery; PO7, patients who took nimodipine by oral (as tablet) in the first week; PCOM, posterior communicating artery; WFNS, World Federation of Neurological Surgeons. [1], (FT7, *n*=24); [2], (PO7, *n*=58).

Most of patients were treated with nimodipine at a dose of 60 mg every four hours; however, 4 patients in the PO7 and 5 patients in the FT7 groups were switched to 30 mg every 2 hours in the first week of nimodipine administration due to reduced blood pressure. Median duration and percentage of nimodipine administration are shown in **Table 2-2**. Both groups had comparable percentages of nimodipine treatment throughout the hospital stay.

Table 2-2: Median duration and percentage of nimodipine administration in the present study

	First 7 days or until discharge (if < 7 days)			**Over 21 days or until discharge (if < 21d)**		
	PO7 (*n* =60)	FT7 (*n* =25)	*p* value	PO21 (*n* =64)	FT21 (*n* =21)	*p* value
No. of days of nimodipine administration	7 (1)	6 (1)	0.234	12 (11)	16 (12)	0.455
% of nimodipine administration overall[1]	100 (14)	86 (14)	0.429	89 (12)	90 (24)	0.653
% of nimodipine administration by FT[2]	0 (0)	100 (25)	<0.001	100 (7)	0 (15)	<0.001
% of nimodipine administration by PO[2]	100 (0)	0 (25)	<0.001	0 (7)	100 (15)	<0.001

Data presented as median (IQR). [1]The median percentage of nimodipine administration was calculated by dividing the number of treatment days by the hospital length of stay in the first week. In addition, for the 21-days full period, the percentage was calculated by dividing the number of days of nimodipine treatment by 21 days or hospital length of stay (if shorter than 21 days). [2]The percentage of nimodipine administration by feeding tube (FT) or orally as whole tables (PO) was calculated by dividing the number of days the patient was given nimodipine by FT or PO, respectively, by the total number of days of nimodipine administration.

2.4.3 Hospital course and clinical outcomes

Out of the 85 patients participated in the study, 8 (9%) patients died and 21 (25%) developed vasospasm (15 patients had angiographic vasospasm; 6 had their vasospasm documented by the managing team in progress notes but their angiography reports were not available). Six patients fitted the criteria of DCI: aphasia and weakness (*n*=1), right sided weakness (*n*=1), left sided weakness (*n*=1), cerebral infarction (*n*=2) and neurological deterioration (*n*=1). All of those who developed DCI had moderate to severe angiographic vasospasm. The median onset days for

angiographic vasospasm and DCI were 7 (IQR 2) and 7 (IQR 4), respectively. The median ICU and hospital length of stay were 12 (IQR 11) and 18 (IQR 25), respectively. A total of 47 (55%) patients needed EVD insertion throughout their stay. With regards to discharge disposition, 50 (59%) patients were discharged home with or without support services and 27 (32%) were transferred to another acute care or continuing care facilities.

2.4.4 The impact of nimodipine administration through enteral feeding tube in the first week on patient outcomes

The impact of nimodipine administration techniques on angiographic vasospasm, DCI and hospital mortality was tested using univariate and multivariate logistic regression models. **Table 2-3** depicts the crude and adjusted odds ratios for predictors of angiographic vasospasm in the best-fit logistic regression model. As shown in the table, after adjusting for disease severity (WFNS, Fisher and APACHE II subscore) and aneurysm intervention, nimodipine administration technique was associated with vasospasm in the first 7 days of patient admission where patients receiving nimodipine via FT had increased odds of angiographic vasospasm compared to those administered it as whole tablets (OR 8.9, 95% CI 1.1-73.1, *p* value 0.042; ROC AUC 0.87, HL-test not significant). In addition, we found that APACHE subscore >15 is also an independent predictor for angiographic vasospasm.

DCI was observed only in patients with Fisher scale III and IV. Therefore, to control for Fisher scale as a confounder in the DCI regression model we analyzed only those with Fisher scale of III and IV (*n* = 58). Administering nimodipine technique was not associated with DCI (OR 18 for FT compared to PO, 95% CI 0.6-570.5, *p* value 0.102; ROC AUC 0.92, HL-test not significant). Furthermore, nimodipine administration technique was not significantly associated with mortality (*p* value 0.087)

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Table 2-3: Crude and adjusted odds ratios of variables included in the final multivariate logistic regression model of angiographic vasospasm in the first week

	Univariate Regression			**Multivariate Regression**		
	OR	*p* value	95% CI	OR	*p* value	95% CI
Nimodipine (FT7)[1]	6.5	0.002	1.9-21.8	8.9	0.042	1.1-73.1
Heavy drinker[2]	2.5	0.179	0.7- 9.9	2.0	0.515	0.3-14.9
Location[3]						
MCA	Ref					
ACOMM	0.8	0.808	0.2 -3.4	4.7	0.224	0.4-57.2
PCOM	1.1	0.895	0.2- 6.4	2.6	0.464	0.2-34.2
Others	0.2	0.117	0.02- 1.6	0.7	0.783	0.0-11.2
Intervention[4]						
Clip	3.0	0.067	0.9-9.4	4.9	0.082	0.8-28.9
Fisher Scale> II[5]	2.3	0.246	0.6-8.9	3.5	0.217	0.5-25.5
WFNS grade >III[6]	2.6	0.116	0.8- 8.7	1.1	0.938	0.1-9.9
APACHE subscore > 15[7]	7.4	0.016	1.5- 37.7	26.4	0.025	1.5-465.7

ACOMM, anterior communicating artery; OR, odds ratio; CI, confidence interval; FT7, took the drug by feeding tube in the first week; WFNS, World Federation of Neurosurgical Societies; MCA, middle cerebral artery; PCOM, posterior communicating artery. [1], compared to whole tablets; [2], compared to those who are not heavy alcohol drinkers; [3], compared to MCA aneurysm location as a reference; [4], compared to endovascular coiling as a reference; [5], compared to those with Fisher Scale ≤ II; [6], compared to those with WFNS grade ≤ III; [7], compared to those with APACHE subscore ≤ 15. A total of 74 patients were included in the multivariate analysis (6 patients excluded due to missing angiography report; 2 missing Fisher scale and 3 had other interventions and excluded by STATA).

2.4.5 The impact of nimodipine administration through enteral feeding tube over 21 days on patient outcomes

As a secondary aim, the impact of nimodipine administration techniques over the 21-days period on angiographic vasospasm, DCI and hospital mortality was tested using logistic regression

modeling. Nimodipine administration by feeding tube was not significantly associated with angiographic vasospasm or mortality over 21 days in patients with SAH. However, among the 58 patients with Fisher scale III-IV, nimodipine administration by feeding tube over the 21-days period was independently associated with DCI (OR 38.1 compared to those receiving whole tablets, 95% CI 1.4-1067.9, *p* value 0.032; ROC AUC 0.94, HL-test not significant) as shown in **Table 2-4**.

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Table 2-4: Crude and adjusted odds ratios of variables included in the final multivariate logistic regression model of DCI over 21 days (Fisher I-II was dropped from analysis)

	Univariate Regression			**Multivariate Regression**		
	OR	*p* value	95% CI	OR	*p* value	95% CI
Nimodipine (FT21)[1]	5.4	0.066	0.9-33.0	38.1	0.032	1.4-1067.9
Age[2]	1.0	0.199	0.9-1.0	0.9	0.193	0.8-1.0
BMI[2]	1.1	0.027	1.01-1.3	1.2	0.157	0.9-1.4
Smoking[3]						
Non-smoker	Ref	0.154	0.0-2.0	Ref	0.334	0.0-9.1
Smoker/Ex-smoker	0.2	0.917	0.1-6.5	0.1	0.755	0.0-17.7
Unknown	0.9			0.6		
WFNS grade >III[4]	1.0	0.975	0.2-6.2	0.2	0.351	0.0-7.1
APACHE II subscore > 15[5]	8.2	0.046	1.04-64.0	18.4	0.174	0.3-1226.4

DCI, delayed cerebral ischemia ; OR, odds ratio; CI, confidence interval; FT21, took the drug by feeding tube over 21 days period; BMI, body mass index; WFNS, World Federation of Neurosurgical Societies; APACHEII, Acute Physiology and Chronic Healthy Evaluation. [1], compared to whole tablets; [2], age and BMI are continous variables; [3], compared to non-smokers as a reference; [4], compared to those with WFNS grade ≤ III; [5], compared to those with APACHE subscore ≤ 15. A total of 57 patients were included in the multivariate analysis (1 patients excluded due to missing BMI value).

2.5 Discussion

In the present study, nimodipine mode of administration was associated with vasospasm in the first week from SAH onset where patients receiving nimodipine via FT had increased odds of moderate to severe angiographic vasospasm compared to those administered it as whole tablets. Furthermore, patients who received nimodipine via feeding tube over the 21 days period were found to have increased odds of DCI compared to those administered whole tablets. To our knowledge, this is the first report suggesting an association between nimodipine technique of oral administration and vasospasm and DCI.

In our institution, all patients presenting with SAH receive oral nimodipine 60 mg every 4 hours for 21 days or until discharge whichever comes first. Patients who have altered mental status, mechanically ventilated or unable to swallow are likely to get nimodipine tablets crushed at bedside and administered immediately through enteral feeding tubes (FT) such as nasogastric or orogastric tubes. The observed associations between nimodipine administration technique and vasospasm and DCI could be attributed to the reduced systemic exposure to nimodipine secondary to reduced oral bioavailability in those getting nimodipine via feeding tubes. The oral bioavailability of nimodipine has been reported to range from 3 to 30% with time to peak concentration ranging from 0.5-1 h (174, 175). Few studies have reported the reduced bioavailability of nimodipine administered through FT in those with high grade SAH (198, 241, 248). Abboud et al have conducted a pharmacokinetic study on nimodipine enteral administration in SAH patients. In patients who were unable to swallow, the tablets were crushed and administered through nasogastric tubes. They have reported that nimodipine exposure as measured by the area under the concentration-time curve (AUC) in the FT group was lower than those who swallowed the whole tablets (median AUC 23.1 vs. 52.3 ng.h/ml, respectively, *p* value 0.006). In

addition, two high grade patients had undetectable plasma levels of nimodipine (248). Similarly, Kumana et al. have reported reduced bioavailability of nimodipine in a patient given crushed tablets through gastric tube (241). Also, Soppi et al have reported lower plasma levels of nimodipine in 3 patients with high grade SAH who were given nimodipine extemporaneously prepared suspension through nasogastric tube (198). None of those studies, however, has reported a correlation between reduced exposure and patient outcomes. Riva et al. have reported an association between nimodipine cerebrospinal fluid concentrations and neurological outcomes at 9 months following SAH onset but they were unable to find such correlation with plasma concentrations (238). It should be noted, however, that all their patients were dosed using nimodipine IV infusion and their plasma concentrations ranged from 24.9 to 71.8 ng/ml, concentrations way above what has been reported in patients given oral dosing (174, 198). Taken together, although the evidence supporting a correlation between nimodipine concentrations and patient outcomes is scarce and not clear but in general, poor absorption of drugs leads to variation in clinical response resulted from the alteration plasma exposure (249-251). Oral nimodipine is also available in other countries as oral capsule and oral suspension. However, it is not clear if the observed reduced bioavailability is a function of the formulation itself, altered pharmacokinetics in SAH patients with high disease severity or both. Reduced bioavailability of drugs secondary to gastrointestinal dysfunction in critically ill patients and those in pain has been reported previously (253, 254). This could explain, at least in part, the reported reduced bioavailability of nimodipine in sicker patients. Intravenous nimodipine was compared to the oral route in two small, randomized trials (239, 240). Both studies have found no difference in patient outcomes; however, the number of patients with high Hunt and Hess grade (IV and V) was small to draw conclusions on the comparability of both routes in high grade patients. Further research is needed.

In the present study, patients who received nimodipine via FT had higher incidence of moderate and severe angiographic vasospasm compared to those who received nimodipine as a whole tablet. On the other hand, most of the randomized controlled trials reporting the benefits of nimodipine on functional outcomes did not show a difference in vasospasm between nimodipine and placebo treated cohorts (156-159). The reason for this discrepancy is unclear and warrants further investigation especially many of the landmark trials did not include high grade patients (Hunt and Hess grades IV and V) where nimodipine is generally given via FT (255). In addition, nimodipine benefit was not demonstrated in patients with Hunt and Hess grade 5 (156). Approximately 7% of our cohort have developed DCI which is lower than what is reported in literature (156-159). This could be attributed to the retrospective chart review design where criteria for DCI may not have been documented in the patient's paper chart underestimating the incidence of DCI. However, each patient has been discussed among authors to confirm the presence or absence of DCI. Despite the reduced prevalence of DCI in our study, FT administration of nimodipine over the 21 days period were associated with DCI.

Our study has limitations. The main limitation is confounding by indication. The group of patients who got nimodipine via FT are generally sicker (higher WFNS grade, Fisher scale and APACHE II subscore), which could have contributed to the observed findings. In addition, the FT group were more likely to get surgical clipping than endovascular coiling further increasing the risk for complications. However, after controlling for those confounders, the association between nimodipine FT administration and worse outcomes still existed, highlighting the need for further investigation. Furthermore, due to the retrospective nature of our study, we were unable to compare the functional outcomes following hospital discharge. A prospective study is recommended to

determine if FT administration is an independent predictor to poor functional outcomes. In addition, the retrospective design is prone to bias, missing data, and confounding. Although we controlled for all possible confounders, we may have not controlled for unknown confounders that may have biased our results. This is a single centre study with small sample size which may limit the generalizability of the findings; however, it warrants conducting a multicentre study to confirm the study findings.

2.6 Conclusion

Our findings suggest that nimodipine administration via enteral feeding tubes may be associated with vasospasm and DCI in subarachnoid hemorrhage patients secondary to reduced exposure. Prospective studies are needed to confirm such association and alternate methods of administration should be explored to ensure patients are getting the benefits of nimodipine.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

References

6. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012;43(6):1711-37.
7. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354(4):387-96.
8. Diringer MN, Bleck TP, Claude Hemphill J, 3rd, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15(2):211-40.
74. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2012;43(6):1711-37.
98. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, et al. Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? Stroke. 2009;40(6):1963-8.
104. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke. 2010;41(10):2391-5.
156. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg. 1988;68(4):505-17.
157. Philippon J, Grob R, Dagreou F, Guggiari M, Rivierez M, Viars P. Acta Neurochir (Wien) (1986) 82:110-114 eCt ahirurgica Prevention of Vasospasm in Subarachnoid Haemorrhage. A Controlled Study with Nimodipine. 1986:110-4.
158. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989;298(6674):636-42.
159. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, et al. Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308(11):619-24.
174. Langley MS, Sorkin EM. Nimodipine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs. 1989;37(5):669-99.
175. Muck W, Ahr G, Kuhlmann J. Nimodipine. Potential for drug-drug interactions in the elderly. Drugs & aging. 1995;6(3):229-42.
198. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage – a pilot study. European Journal of Clinical Pharmacology. 2007;63:355-61.
238. Riva R, Pegoli M, Contin M, Perrone A, Mohamed S, Zanello M. Cerebrospinal Fluid Concentrations of Nimodipine Correlate With Long-term Outcome in Aneurysmal Subarachnoid Hemorrhage: Pilot Study. Clin Neuropharmacol. 2019.

239. Soppi V, Karamanakos PN, Koivisto T, Kurki MI, Vanninen R, Jaaskelainen JE, et al. A randomized outcome study of enteral versus intravenous nimodipine in 171 patients after acute aneurysmal subarachnoid hemorrhage. World Neurosurg. 2012;78(1-2):101-9.
240. Kronvall E, Undren P, Romner B, Saveland H, Cronqvist M, Nilsson OG. Nimodipine in aneurysmal subarachnoid hemorrhage: a randomized study of intravenous or peroral administration. J Neurosurg. 2009;110(1):58-63.
241. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European journal of clinical pharmacology. 1993;45(4):363-6.
246. Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. Crit Care. 2016;20(1):277.
247. NIMOTOP(R) Product Monograph, Mississauga, Ontario. Bayer Inc.; 2014.
248. Abboud T, Andresen H, Koeppen J, Czorlich P, Duehrsen L, Stenzig J, et al. Serum levels of nimodipine in enteral and parenteral administration in patients with aneurysmal subarachnoid hemorrhage. Acta Neurochirurgica. 2015;157(5):763-7.
249. Bardelmeijer HA, van Tellingen O, Schellens JH, Beijnen JH. The oral route for the administration of cytotoxic drugs: strategies to increase the efficiency and consistency of drug delivery. Invest New Drugs. 2000;18(3):231-41.
250. Beierle I, Meibohm B, Derendorf H. Gender differences in pharmacokinetics and pharmacodynamics. Int J Clin Pharmacol Ther. 1999;37(11):529-47.
251. Katsura T, Inui K. Intestinal absorption of drugs mediated by drug transporters: mechanisms and regulation. Drug Metab Pharmacokinet. 2003;18(1):1-15.
252. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
253. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin. 2006;22(2):255-71, vi.
254. Jamali F, Kunz-Dober CM. Pain-mediated altered absorption and metabolism of ibuprofen: an explanation for decreased serum enantiomer concentration after dental surgery. Br J Clin Pharmacol. 1999;47(4):391-6.
255. Dorhout Mees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007(3):CD000277.

Chapter 3 Enantioselective Assay of Nimodipine in Human Plasma using Liquid Chromatography – Tandem Mass Spectrometry

This paper has been Published

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Keywords: Nimodipine, liquid chromatography, tandem mass spectrometry, LC- MS/MS, human plasma

3.1 Abstract

Nimodipine is a dihydropyridine calcium channel blocker that exhibits higher selectivity towards cerebral blood vessels compared to other members of the same class. It has been shown to improve outcomes and prevent delayed cerebral ischemia in the setting of aneurysmal subarachnoid hemorrhage, a life-threatening brain bleed. Nimodipine is a chiral compound and it is marketed as a racemic mixture of (+)-R and (-)-S enantiomers. (-)-S nimodipine is approximately twice as potent vasorelaxant as the racemic mixture and is more rapidly eliminated than (+)-R counterpart following oral dosing. Few analytical procedures have been reported to determine nimodipine enantiomers in biological samples; however, the reported methods were time-consuming, involved multi-step extraction procedures and required large sample volumes. Herein, we present an LC-MS/MS method for quantifying nimodipine enantiomers in human plasma using a small sample volume (0.3 ml) and a single liquid-liquid extraction step. The peak area ratios were linear over the tested concentration ranges (1.5-75 ng/ml) with $r^2 > 0.99$. The intraday CV and percentage error were within ±14% while the interday values were within ±13%, making this analytical method feasible for research purposes and pharmacokinetic studies.

3.2 Introduction

Nimodipine, 3-O-(2-methoxyethyl) 5-O-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, is a dihydropyridine calcium channel blocker with vasodilating properties. Nimodipine exhibits higher selectivity towards cerebral blood vessels compared to other members of the class. As a result, nimodipine has been shown to improve outcomes and prevent delayed cerebral ischemia in the setting of aneurysmal subarachnoid hemorrhage, a life-threatening brain bleed (156-159). Nimodipine is a chiral compound with an

asymmetric carbon at position 4 of the dihydropyridine ring structure (**Figure 3-1**) and it is marketed as a racemic mixture of (+)-R and (-)-S enantiomers. Towart et al have found that (-)-S nimodipine is approximately twice as potent vasorelaxant as the racemic mixture (169). In addition, the (-)-S enantiomer is more rapidly eliminated than (+)-R counterpart following oral dosing resulting in a significantly lower (-)-S enantiomer concentration (184, 187, 245). Stereochemistry is a crucial knowledge to incorporate in the growing laboratory analytical methods and it is extremely important to emphasize the significance of using enantioselective assays when determining the effectiveness and adverse effect profiles or studying the disposition of chiral therapeutic agents. Several analytical procedures have been reported to determine nimodipine concentrations in biological samples utilizing various techniques including gas chromatography, high-performance liquid chromatography and liquid chromatography tandem mass spectrometry (LC-MS/MS) (184, 187, 208, 211, 245, 256-258). However, the majority of the methods in literature were non-enantioselective. Three methods have reported enantioselective assay for nimodipine (184, 187, 245). However, the reported methods were time-consuming, involved multi-step extraction procedures and required large sample volumes. Herein, we present an LC-MS/MS method for quantifying nimodipine enantiomers in human plasma using a small sample volume and a single liquid-liquid extraction step, making this analytical method feasible for research purposes and pharmacokinetic studies.

3.3 Experimental

3.3.1 Chemicals and Reagents

The reference analyte nimodipine (purity ≤ 100 %), internal standard (IS) nifedipine (purity ≥ 98%) (**Figure 3-1**), HPLC grade water and hexane and sodium hydroxide were purchased from

Sigma-Aldrich (Oakville, Ontario, Canada). Methanol HPLC grade and ethyl ether anhydrous were obtained from Fisher Scientific (Edmonton, Alberta, Canada). Blank human plasma was obtained from Cedarlane Laboratories (Burlington, Ontario, Canada).

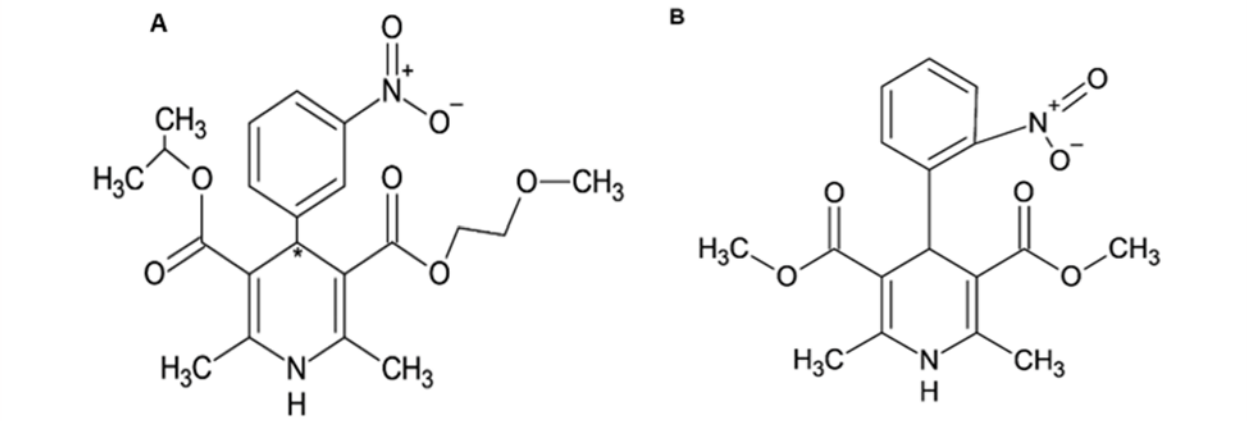

Figure 3-1: Chemical structure of nimodipine (A) and nifedipine (B).

3.3.2 Instrument

The experiment was performed using an LC-MS/MS system (Shimadzu, Kyoto, Japan) with a CBM-20A system controller, DGU-20A 5R degasser unit, SIL-30-AC autosampler, LC-30 AD binary pump, CTO-20 AC column oven and LCMS-8050 triple quadrupole mass spectrometry detector. The chromatographic separation was carried out by using (S, S)-Whelk O1 (5µm, 250×4.6 mm) chiral stationary phase column (Regis Technologies Inc., Morton Grove, Illinois, USA) with KrudKatcher® Ultra guard column (Phenomenex, Torrance, California, USA). LabSolutions® software version 5.91 (Shimadzu Kyoto, Japan) was utilized for data acquisition and chromatographic integration.

3.3.3 Liquid Chromatography -Tandem Mass Spectrometry Conditions

A mobile phase consisting of methanol and water (75:25, v/v) with a flow rate of 1 ml/min was used for the elution of both the analyte and IS and run time was 25 min. The autosampler and column oven temperatures were kept at 4 and 40 ºC, respectively. A triple quadrupole mass spectrometry detector operated with positive mode electrospray ionization source (ESI+) along with multiple reaction monitoring (MRM) was used to analyze the samples. The MRM mass transitions (m/z for precursor and product ions) were 419.24→343.15 for nimodipine and 347.15→315.20 for nifedipine. The collision energy (CE) was 10 V for nimodipine and 9 V for nifedipine. The interface and conversion dynode voltages were 4 and 10 kV, respectively. The temperatures of desolvation line, heat block and interface were 250, 400 and 300 ºC, respectively. The nebulizing, drying, and heating gas flows were 2, 10, and 10 L/min, respectively.

3.3.4 Standard Stock and Working Solutions

Nimodipine and nifedipine were dissolved in methanol and 1mg/ml standard stock solutions were prepared and stored at 4C°. Standard stock solutions were stable for at least two weeks. Working solutions of 1000 ng/ml and 100 ng/ml of nimodipine were freshly prepared each day. Internal standard solution of nifedipine 50 ng/ml was freshly prepared daily. Standard and working solutions were prepared under dim light conditions and covered with aluminum foil to avoid photodegradation of the analytes.

3.3.5 Calibration Standards and Quality Control Samples

Serial dilutions of racemic nimodipine concentrations in blank human plasma ranging from 3-150 ng/ml (1.5-75 ng/ml per enantiomer) were prepared to construct nimodipine calibration curves. Four quality control (QC) samples were prepared along with the calibration concentrations to validate our method: Lowest limit of quantification (LLOQ), a low level LQC (3× LLOQ), a

middle level MQC (around the middle of the range of calibration concentrations) and high level HQC (around 75-95% of the upper limit of quantification).

3.3.6 Sample Preparation

All procedures were carried out under dim light conditions to avoid photodegradation of the analytes. A 300 µl plasma was mixed with 50 µl of 50 ng/ml nifedipine (IS). Samples were vortex mixed for 1 min. A 200 µl of 1M sodium hydroxide was then added to the samples and vortex mixed for 1 min. Then, 4 ml of hexane and diethyl ether (1:1, v/v) was added to the samples. Mixtures were then put in a test tube-shaker and vortex mixed for 5 minutes, and then centrifuged at 2000 rpm for 10 minutes at room temperature. The organic layer was then transferred to clean test tubes and dried by SpeedVac® Vacuum Concentrator (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Residue was reconstituted by 125 µl mobile phase (methanol: water, 75:25, v/v) and vortexed for 10 sec. The reconstituted samples were transferred to amber micro-vials and capped and a 40 µL volume of the reconstituted sample was injected into the LC-MS/MS.

3.4 Method Validation

For method validation, linearity, selectivity, sensitivity, precision, accuracy, extraction recovery and matrix effect were evaluated.

3.4.1 Linearity

The linearity of the method was assessed by constructing calibration curves by plotting peak area ratios (nimodipine/internal standard) vs. the nominal concentrations of the calibration standards (1.5, 2.5, 5, 12.5, 50 and 75 ng/ml). Linear regression was used to calculate the slope, intercept, and the coefficient of determination (r^2) for each calibration curve.

3.4.2 Selectivity and Sensitivity

Blank human plasma samples were injected before each run. Selectivity was assured by the absence of peaks at the retention times of the analyte and IS when blank samples were injected. LLOQ was the lowest concentrations in the calibration curve with precision < 20% and accuracy within ±20%. In addition, the signal of the LLOQ had also to be at least 5 times higher than that of blank plasma signal.

3.4.3 Precision and Accuracy

The accuracy and precision of the method were evaluated by analyzing five replicates of QC samples spiked with nimodipine at 4 QC levels (1.5, 4.5, 12.5 and 62.5 ng/ml) in three separate runs over 3 days. The precision was presented as coefficient of variation (CV, %) while the accuracy was expressed as percent error (%, error). Intraday and Inter-day performance of the method was evaluated.

3.4.4 Recovery and Matrix Effect

To assess the mean extraction recovery, the peak areas of the extracted samples at LQC and MQC levels were compared with those obtained from extracts of blank plasma spiked with equivalent concentrations of nimodipine post-extraction. The matrix factor (MF) was also assessed by calculating the ratio of the peak area of the analytes in the presence of matrix (obtained from extracts of blank plasma spiked with the analytes post-extractions) to the peak area of equivalent concentrations in the absence of matrix (pure samples). The IS-normalized MF was determined by dividing the MF of nimodipine by the MF of the IS nifedipine. The CV of the IS-normalized MF was calculated from three samples at 2 QC levels (4.5 and 62.5 ng/ml).

3.4.5 Method application

We applied our method in the analysis of plasma concentrations obtained from an aneurysmal subarachnoid hemorrhage patient. Written informed consent was obtained and the study was approved by the Health Research Ethics Board (HERB) of the University of Alberta.

3.5 Results and discussion

3.5.1 LC-MS/MS method development

We used the LC-MS/MS tool because of its unique specificity and selectivity. Multiple reaction monitoring mode was set up to monitor the precursor and product ions of our interest. Optimization of the method and the condition of the MS/MS has been performed manually via flow injection analysis. Nimodipine and nifedipine (IS) resulted in a protonated precursor ion [MH]+ with m/z 419.25 and 347.15 for nimodipine and nifedipine, respectively. The highest signal intensity was found for product ions m/z= 343.15 and m/z= 315.20 for nimodipine and IS, respectively. Positive electrospray ionization mode (+ESI) was the suitable technique for our analyte and IS for ion generation. Both negative and positive polarities were tested. Also, ESI and atmospheric pressure chemical ionization (APCI) together and alone were explored. ESI+ mode was superior to give higher intensity signal peak. Other parameters including the collision energy, ionization mode and interface voltage were also optimized. Different mobile phase compositions were also tried with or without formic acid. Binary isocratic elution containing a mobile phase of methanol and water (75:25, v/v) was found to assure enough separation of the two enantiomers and with acceptable retention times. The (-)-S and (+)-R enantiomers were eluted at 17.5 and 19.4 minutes, respectively **(Figure 3-2)**. To our knowledge, there is not any information in the literature regarding the interconversion between (+)-R and (-)-S enantiomers during storage and analysis. Also, we have not tested this in our assay as we were not able to obtain individual enantiomers. Nevertheless, in

our analysis, running standard nimodipine samples always provided equivalent ratios of the peaks of the two enantiomers suggesting that in vitro chiral conversion is less likely.

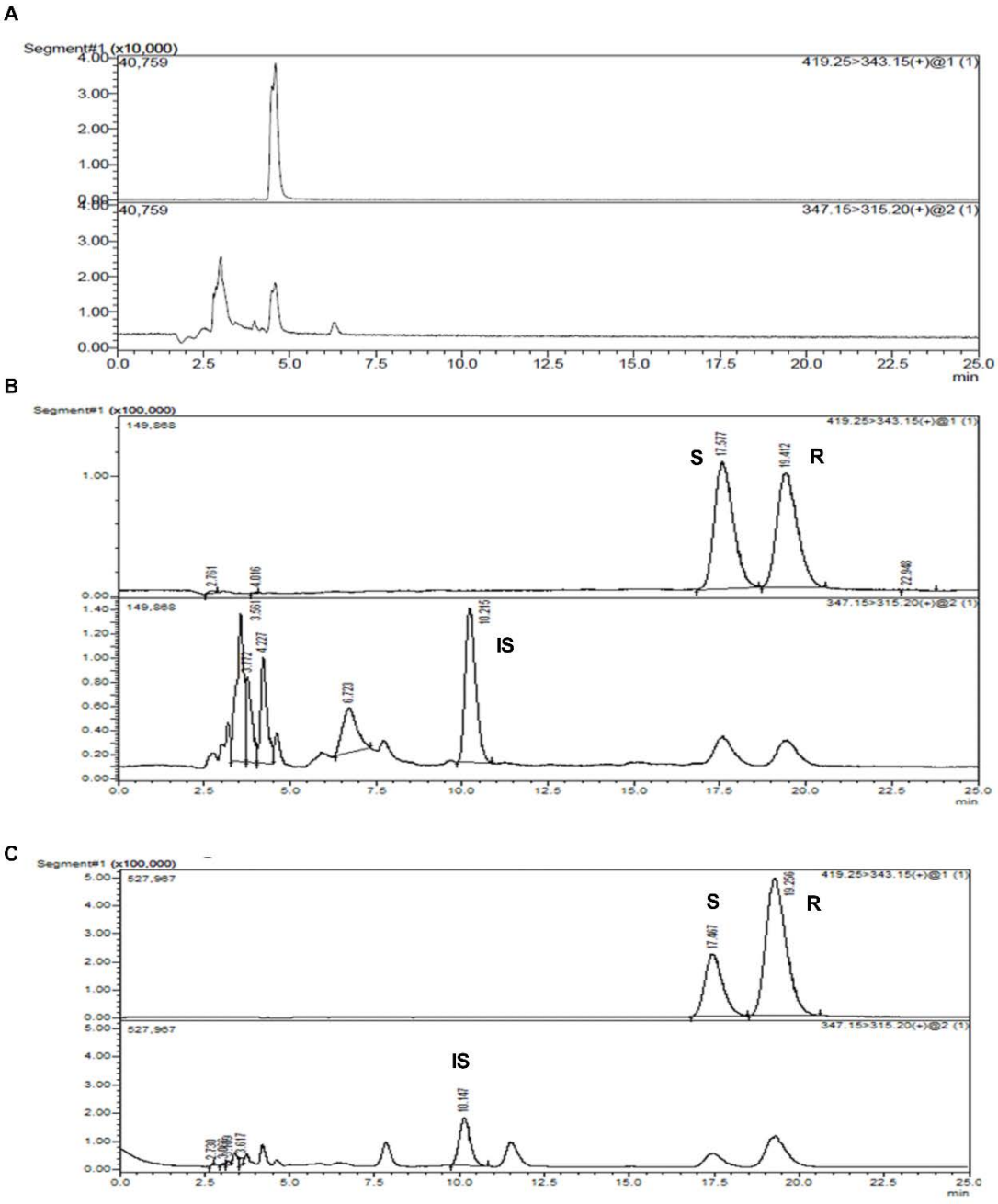

Figure 3-2: Chromatogram of MRM set up for nimodipine (±) (429.25>343.15) and for nifedipine in blank plasma (347.15>315.20). A, blank plasma; B, blank plasma spiked with 5 ng/ml nimodipine; C, a plasma sample of an aneurysmal subarachnoid hemorrhage patient drawn 0.5h following nimodipine 60 mg oral dose. IS, internal standard peak.

3.5.2 Method Validation

3.5.2.1 Linearity

The linearity of the method was assessed by running both pure and extracted samples over the concentration ranges of nimodipine. The peak area ratios were linear over the tested concentration ranges (1.5-75 ng/ml) with $r^2 > 0.99$ and weighting factor of ($1/x^0$) (**Figure 3-3**).

3.5.2.2 Selectivity and Sensitivity

There were no interfering peaks with both nimodipine and nifedipine (**Figure 3-2A**). In addition, there were no carryover effects when we ran blank plasma, mobile phase and HPLC water multiple times in the beginning of the run and in between runs. The LLOQ was found to be 1.5 ng/ml for each enantiomer with inter- and intraday accuracy and precision within ±12%.

3.5.2.3 Precision and Accuracy

The intraday and interday performance of the method were evaluated by analyzing five replicates of QC samples spiked with nimodipine at 4 QC levels. As shown in **Table 3-1**, acceptable intraday and inter-day CV and percent error were achieved. The intraday variation and percentage error were within ±14% while that of the interday was within ±13%.

3.5.2.4 Recovery and Matrix Effect

Various extracting solvents and different volumes have been tried. Hexane, diethyl ether, dichloromethane alone and in combination were tested for their extracting efficiency. A 4 ml containing both hexane and diethyl ether (1:1, v/v) provided the best extraction recovery from human plasma. The recovery was 75.3±5.8 and 73.1±2.4 % for (-)-S and (+)-R enantiomers, respectively at MQC and was 77.4±7.6 and 81.4±6.1 % for (-)-S and (+)-R enantiomers, respectively at HQC. Although did not reach 100%, extraction recovery was sufficient to analyze

nimodipine enantiomer concentrations with reasonable accuracy and precision. With regards to matrix effect, the CVs of the IS-normalised MF (n =3) for both enantiomers were < 13 %.

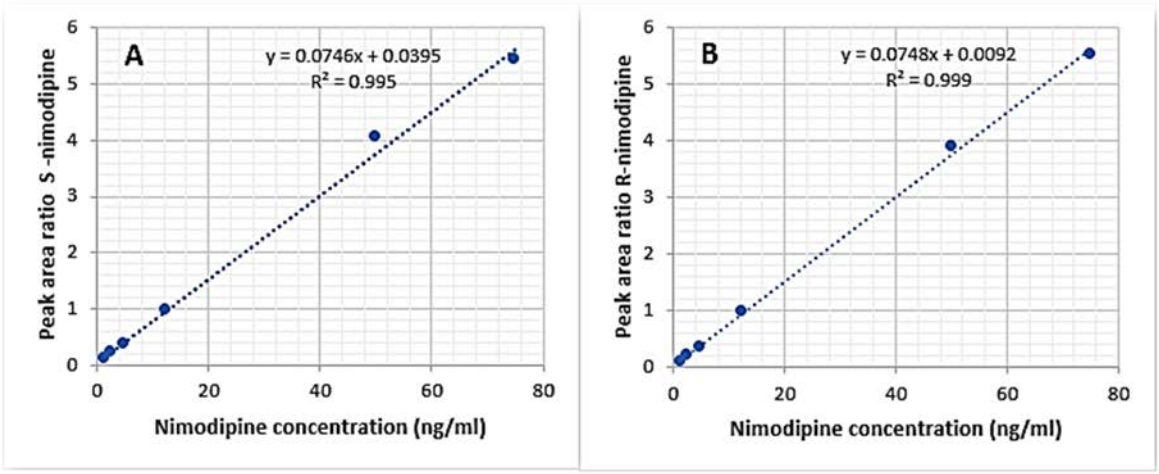

Figure 3-3: A, representative calibration curve of S- nimodipine; B, representative calibration curve of R- nimodipine over the range of 1.5-75ng/ml.

Table 3-1: Precision and accuracy for nimodipine (±) QC samples in human plasma

	QC conc.	Measured concentration (ng/ml) *		Precision CV (%)		Accuracy Error (%)	
	ng/ml	(+)-R	(-)-S	(+)-R	(-)-S	(+)-R	(-)-S
Intraday (n=5)	1.5	1.3± 0.1	1.5 ± 0.1	5.5	7.5	-10.3	0.3
	4.5	4.5 ± 0.1	4.6 ± 0.3	1.6	6.4	0.7	3.2
	12.5	12.3± 0.3	11.9 ± 0.8	10.7	7	-1.7	-5
	62.5	62.3±8.1	64.3 ± 8.9	13.1	13.8	-0.3	2.9
Interday (n=15)	1.5	1.5 ± 0.2	1.7± 0.2	11.4	9.2	3.0	11.0
	4.5	5.1 ± 0.5	5.0 ± 0.4	10.1	7.9	12.7	12.0
	12.5	13.4 ± 1.0	13.3 ± 1.3	7.4	9.8	7.1	6.6
	62.5	61.3 ± 0.9	63.1 ± 3.2	1.5	5.1	-2	1

*, Mean ± SD

3.5.2.5 Method Application and Identification of Individual Enantiomers

The validated method was applied in analyzing nimodipine enantiomers plasma concentrations in a SAH patient (**Figures 3-2C** and **3-4**). Samples were collected 0–3h after administration of a 60 mg nimodipine oral dose. The (-)-S enantiomer undergoes more extensive hepatic metabolism than the (+)-R counterpart. As a result, the plasma concentrations of (+)-R are much higher than those of the (-)-S enantiomer following oral dosing and this has been consistently reported in literature (184, 187, 245). Given that, we were able to identify the (-)-S and (+)-R enantiomer peaks as analysis of patient samples resulted in that the first peak is the lower peak, corresponding to the (-)-S enantiomer followed by the peak of the R-enantiomer.

3.6 Conclusion

Herein, we report a simple and practical method for determination of nimodipine enantiomers in human plasma. The method is sensitive and selective and can accurately and precisely quantify nimodipine enantiomers over the concentration ranges of 1.5-75 ng/ml.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

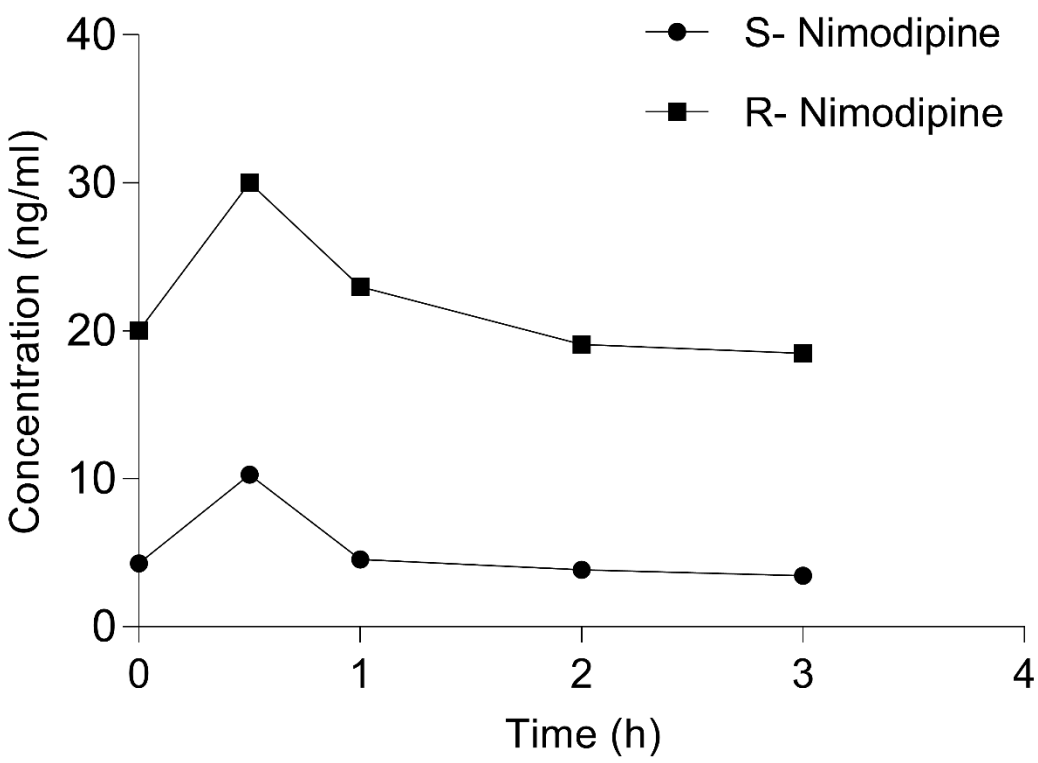

Figure 3.1: Steady state nimodipine enantiomers plasma concentrations vs time curve in an aneurysmal subarachnoid hemorrhage patient following a 60 mg oral dose (patient is being treated with 60 mg po every 4 hours for 2 days before sampling)

References

156. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg. 1988;68(4):505-17.
157. Philippon J, Grob R, Dagreou F, Guggiari M, Rivierez M, Viars P. Acta Neurochir (Wien) (1986) 82:110-114 eCt ahirurgica Prevention of Vasospasm in Subarachnoid Haemorrhage. A Controlled Study with Nimodipine. 1986:110-4.
158. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989;298(6674):636-42.
159. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, et al. Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308(11):619-24.
169. R.Towart EW, H.Meyer, and S.Kazda. The Effect of Nimodipine, its Optical Isomers and Metabolites on Isolated Vascular Smooth Muscle. ArzneimForsch/Drug Res. 1982;32(1):338-46.
184. Fischer C, Schonberger F, Muck W, Heuck K, Eichelbaum M. Simultaneous assessment of the intravenous and oral disposition of the enantiomers of racemic nimodipine by chiral stationary-phase high-performance liquid chromatography and gas chromatography/mass spectroscopy combined with a stable isotope technique. J Pharm Sci. 1993;82(3):244-50.
187. Wanner-Olsen H, Gaarskaer FB, Mikkelsen EO, Jakobsen P, Voldby B. Studies on concentration-time profiles of nimodipine enantiomers following intravenous and oral administration of nimodipine in patients with subarachnoid hemorrhage. Chirality. 2000;12(9):660-4.
208. Qin F, Ma Y, Wang Y, Chen L, Wang D, Li F. Determination of nimodipine in human plasma by ultra performance liquid chromatography-tandem mass spectrometry and pharmacokinetic application. Journal of Pharmaceutical and Biomedical Analysis. 2008;46(3):557-62.
211. Zhao Y, Zhai D, Chen X, Yu Q, He H, Sun Y, et al. Determination of nimodipine in human plasma by HPLC-ESI-MS and its application to a bioequivalence study. Journal of Chromatographic Science. 2010;48(2):81-5.
245. Muck WM. Enantiospecific determination of nimodipine in human plasma by liquid chromatography-tandem mass spectrometry. Journal of Chromatography A. 1995;712(1):45-53.
256. Krol GJ, Noe AJ, Yeh SC, Raemsch KD. Gas and liquid chromatographic analyses of nimodipine calcium antagonist in blood plasma and cerebrospinal fluid. J Chromatogr. 1984;305(1):105-18.
257. Mohamed S, Riva R, Contin M. Simple and validated UHPLC-MS/MS analysis of nimodipine in plasma and cerebrospinal fluid of patients with subarachnoid haemorrhage. J Chromatogr B Analyt Technol Biomed Life Sci. 2016;1028:94-9.
258. do Nascimento DF, de Moraes MO, Bezerra FAF, Pontes AV, Uchoa CRA, de Moraes RA, et al. Determination of nimodipine in plasma by HPLC-MS/MS and pharmacokinetic application. Brazilian Journal of Pharmaceutical Sciences. 2010;46(4):665-77.

Chapter 4 Nimodipine Exposure and Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage: A Prospective Pilot Study

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4.1 Abstract

PURPOSE: Nimodipine has been shown to improve outcomes following aneurysmal subarachnoid hemorrhage (SAH), a life-threatening illness. Guidelines recommend that all patients receive nimodipine fixed doses for 21 days. However, pharmacokinetic studies reported extensive variability of nimodipine concentrations in SAH. It is not clear if minimal systemic exposure to nimodipine affects on its clinical benefit and contributes to worsening patient outcomes. **OBJECTIVES**: The primary objective of this pilot study was to preliminarily determine potential factors that might have an influence on nimodipine exposure. The secondary objective was to preliminarily investigate whether there is a trend of possible association between nimodipine exposure and patient outcomes. **METHODS**: A prospective observational pilot study of adult patients diagnosed with SAH and admitted to the University of Alberta Hospital. Blood samples were collected following a single nimodipine 60 mg dose at steady state at 0 (just before the dose), 0.5, 1, 2- and 3-hours following administration. Plasma nimodipine enantiomers concentrations were quantified using the LC-MS/MS method that we validated. Area under the concentration-time curve ($AUC_{0\text{-}4h)}$ was calculated. Factors that could influence plasma nimodipine drug concentrations were assessed in different patient categories. Both discharge outcomes and 3-months Modified Rankin (mRS) were collected. **RESULTS**: Patients who took nimodipine through feeding tubes and those with high grade disease had a trend for lower systemic exposure. On the other hand, older patients had higher nimodipine exposure compared to younger ones. With regards to outcomes, this pilot study preliminarily determined that the median $AUC_{0\text{-}4h}$ values for both nimodipine enantiomers were lower in the 2 patients who had developed vasospasm. There was also a trend for a lower (+)-R nimodipine exposure for patients who had modified Rankin Scale of 3 (worse outcome) than those who had an mRS of 1 Scale 1 (better outcome).

CONCLUSIONS: This pilot study suggested that nimodipine systemic exposure might be association with outcomes in SAH patients. A larger prospective multicenter study is recommended.

4.2 Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a life-threatening neurological emergency resulting from a ruptured brain aneurysm. The incidence of this type of stroke is only 5-10%. Despite the lower incidence compared to ischemic stroke, it results in the death of up to 50% of the patients (2). Early multidisciplinary care and specialized intervention to secure the leaking blood vessel is the most critical life saving response for these patients. Upon effective management of the burst blood vessel, the second most important care is to prevent complications that can negatively affect patient outcomes. The two most feared and common complications are cerebral vasospasm and delayed cerebral ischemia (DCI) (92, 102, 103). The standard care of prevention of those complications is treating them with the dihydropyridine calcium channel blocker, nimodipine (148, 149). As the mechanism of nimodipine described in **CHAPTER 1**, the drug's benefit is well known in SAH patients to protect against delayed cerebral ischemia consequently improving patient outcomes(156-159) .

Guidelines recommend that all patients presenting with aneurysmal SAH should receive a fixed dose of oral nimodipine 60 mg every 4 hours for 21 days from SAH onset (8). In a literature review carried out by our team, extensive variability of nimodipine concentrations in various populations and in the setting of SAH was reported, with some patients had undetectable nimodipine plasma levels (190, 194, 198, 200, 225). To illustrate, Soppi et al have reported nimodipine concentrations following the standard 60mg po Q4H dosing schedule in SAH patients (198). Nimodipine maximum concentrations ranged from as low as 1 ng/ml up to 56.7 ng/ml for those receiving

tablets and 0.9-1.7 ng/ml for those receiving an oral suspension. Similarly, Abboud et al compared plasma nimodipine concentrations administered parenterally followed by enteral administration. The area under the concentration time curve (AUC) of the parenteral route was significantly higher than that of the oral route. Moreover, nimodipine AUC for those who swallowed whole nimodipine tablets was higher than those who received it through enteral feeding tube [median 52 (IQR 26–1411) ng.h/ml vs. 23 (IQR 6-1272 ng.h/ml), respectively, *p*-value 0.006] (190). In addition, two patients with high grade SAH had undetectable nimodipine concentrations. The observed variability in nimodipine exposure may have been attributed to practice variations in nimodipine administration, systemic inflammation, disease severity, administration of concomitant interacting drugs and cytochrome P450 polymorphism (187, 210, 236, 237).

While previous randomized controlled trials have found that nimodipine reduces the incidence of poor neurologic outcomes (defined by death, persistent vegetative state, and severe disability) by 40-86%, still up to 22 % patients in the nimodipine arm experienced poor outcomes.(156, 158, 159) Therefore, it is not clear if all patients are getting the full benefit of nimodipine using a fixed dose regimen. However, no previous studies have addressed if an association exists between plasma nimodipine concentrations after oral dosing and clinical outcomes.

The primary objective of this pilot study was to preliminarily determine potential factors that might have an influence on nimodipine exposure. The secondary objective was to preliminarily investigate whether there is a trend of possible association between nimodipine exposure and patient outcomes (vasospasm, DCI, and modified Rankin Scale (mRS) at 90 days post SAH admission). We hope the preliminary findings of this pilot study to lay the foundation of a larger prospective observational study to investigate the association between nimodipine exposure and patient outcomes.

4.3 Methods

4.3.1 Study Design

A prospective observational pilot study of adult patients diagnosed with SAH and admitted to the University of Alberta Hospital, Edmonton. The study enrollment started in June 2019. The study was approved by the Health Research Ethics Board (HERB) of the University of Alberta and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent was mandatory.

4.3.2 Study Population

Adult patients admitted to the Neuroscience Intensive Care Unit (ICU) and the high intensity unit (HIU) at the University of Alberta Hospital for aneurysmal subarachnoid hemorrhage were recruited. **Table 4-1** depicts the study's inclusion and exclusion criteria.

Table 4-1: Participant Eligibility Criteria

Inclusion criteria	**Exclusion criteria**
Age 18-85 years	Anticipated ICU length of stay < 48h
Adult patients admitted to the ICU or HIU at the University of Alberta Hospital	Non-aneurysmal SAH
Diagnosis of aneurysmal subarachnoid hemorrhage	Not treated with nimodipine
Provision of informed consent by patient or legal representative	
Treated with nimodipine 60 mg PO/FT Q4H from admission and at the time of blood sampling	

4.3.3 Baseline Data Collection

Patients' demographics (age, sex, height, weight, and body mass index (BMI)), past medical history (history of diabetes, hypertension, kidney and liver disease, migraine, baseline disability mRS, other comorbidities, and home medications) and social history (smoking and alcohol intake) were captured. In addition, admission Glasgow coma scale (GCS), World Federation of Neurological Surgeons (WFNS) grade, Fisher scale, Acute Physiology and Chronic Health Evaluation (APACHE II) score, aneurysm location, and aneurysm intervention (surgical clipping, endovascular coiling or other). APACHE II physiological sub-score was obtained by subtracting GCS and age from APACHE II score. Nimodipine administration reports such as dose, interval, days of treatment, method of administration (swallowed whole tablets (PO) vs being crushed and administered by enteral feeding tube (FT)) and any deviations from normal dosing or missing dose were obtained. In addition, administration of interacting drugs (cytochrome P450 enzyme inducers and inhibitors) was collected. The study measurements including current dose and route, dose time, sampling date, day of sampling from the treatment initiation, actual sampling time (hours) were also documented. All data collected within the context of this study were anonymized and kept in an electronic format and in REDCAP database. REDCap is an encrypted, password protected, online data server. All electronic files containing study data will be password protected.

4.3.4 Outcome Data Collection

The outcome collected at the discharge were: in-hospital development of vasospasm, delayed cerebral ischemia (DCI), Hospital mortality, and discharge disposition (home, transfer to subacute care facility, dead). Modified Rankin Scale (mRS) (**Table 4-2**) was collected by contacting the participant or their legal authorized representative at 90 days following SAH admission. DCI was defined according to Vergouwen et al as "The occurrence of focal neurological impairment (such

as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies".(104) Vasospasm was defined as the presence of angiographic evidence of cerebral arterial narrowing.

Table 4-2: Modified Rankin Scale (mRS)(259)

Outcome	Score	Definition
Favorable	0	No symptoms
Outcome	1	No significant disability despite symptoms; able to carry out all usual duties and activities
	2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
	3	Moderate disability: requiring some help, but able to walk without assistance
Poor	4	Moderately severe disability: unable to walk without assistance and unable
Outcome		to attend to own bodily needs without assistance
	5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
	6	Dead

4.3.5 Sample Collection and Analysis

Once patients or their legal authorized representative consented to the study, participants had blood samples collected for determination of nimodipine plasma concentrations. Blood samples were collected around one nimodipine 60 mg dose within 2-7 days after initiation. In our institution, nimodipine is always started shortly after SAH diagnosis is confirmed (<24h). Therefore, nimodipine concentrations are considered at steady state on the day of sampling. Blood samples (5 ml each) were collected at 0 (just before the dose), 0.5, 1, 2 and 3 hours following the administration of nimodipine. Samples were collected by the bedside nurse in foil wrapped blood collection tubes (K2EDTA Vacutainer® lavender top, BD, San Jose, CA, USA). Blood samples were drawn through an already established intravascular catheter. The samples were labelled appropriately, protected from the light, and immediately transferred to the laboratory for centrifuging. Plasma samples were then stored at -80°C until analysis. Plasma nimodipine concentrations were quantified with a validated enantio-selective method by using liquid chromatography – tandem mass spectrometry (LC-MS/MS). All sample processing was carried out under dim light conditions. Patient plasma samples were mixed with 50 µl of 50 ng/ml nifedipine (IS). Samples were vortex mixed for 1 min. A 200 µl of 1M sodium hydroxide was then added to the samples and vortex mixed for 1 min. Then nimodipine was extracted from the plasma of the patients by one step liquid-liquid extraction with 4 ml of hexane and diethyl ether (1:1, v/v). The samples were then dried and reconstituted. The samples were then injected to the LC-MS/MS for analysis.

4.3.6 Data Analysis

Patients' baseline characteristics were summarized. Continuous variables were presented as mean± standard deviation or median ± interquartile range, as appropriate. Categorial variable will be presented as frequency and percentage, n (%). Non compartmental analysis was performed. The $AUC_{0\text{-}4h}$ was determined using a linear trapezoidal method (given that sampling was done at steady state and nimodipine was administered every 4 hours, concentration values at time 0 were also included as time 4h) . The C_{max} was determined as peak concentration that a drug achieved. C_{min} was determined to be the minimum (or trough) concentration.

The contribution of various covariates on nimodipine exposure in patients with SAH was determined. Covariates were evaluated by categorization. Covariates examined included age, sex, presence of interacting drugs, liver disease, SAH grade (disease severity), body weight and nimodipine technique of administration (whole tablets vs. administration by FT). Due small sample size we were not able to conduct inferential statistics; however, we were able to identify trends that will be useful in design of the larger prospective study. The trend of nimodipine exposure with the outcome was performed the same as the potential factor analysis. By sorting the classification of the outcomes, we calculated the median of $AUC_{0\text{-}4h}$ of each particular outcome and comparison was made to find if nimodipine exposure was different.

4.4 Results

4.4.1 Baseline Patient Characteristics

Patient baseline characteristics are depicted in **Table 4-3**. The dosage regimen was either 60mg q4h or 30mg q2h administered as a tablet or as crushed tablets through feeding tubes. Eight patients were enrolled into the study. One patient was excluded due to missing 3 blood samples. Therefore, 7 patients were included in the analysis (Four females, three males, mean age of 62 ±

11 years, range 48-79 years). The mean body weight was 90 kg; three patients were obese (≥30 kg/m^2). None of the patients had history of kidney or liver disease. The baseline modified Rankin Scale for all patients was (0) and the median (IQR) of admission GCS, was 14 (2). Only two patients had high grade WFNS (IV-V). In addition, four patients had their aneurysm treated with endovascular coiling and three patients underwent surgical clipping.

Table 4-3: Baseline characteristics of patients included in the pilot study

	(n=7)
Age, mean ± SD	62 ± 11
Female sex, n (%)	4 (57)
Height (cm), mean ± SD	176 ± 19
Weight (kg), mean ± SD	90 ± 25
BMI, mean ± SD	29 ± 7
BMI categories, n (%)	
17-24.9 kg/m^2	2 (29)
25-29.9 kg/m^2	2 (29)
≥30 kg/m^2	3 (43)
Medical history	
Hypertension, n (%)	2 (29)
Smoking history, n (%)	
Non-smoker	3 (43)
Smoker	2 (29)
Ex-smoker	1 (14)
Unknown	1 (14)
Alcohol history, n (%)	
Occasional drinker	3 (43)
Non-drinker	2 (29)
Un-known	2 (29)
SAH characteristics, n (%)	
Location	
MCA	1 (14)
ACOMM	2 (29)
PCOM	1 (14)
Others	3 (43)
Intervention	
Coil	4 (57)
Clip	3 (43)
Fisher Scale	
I-II	2 (29)
III-IV	5 (71)
WFNS grade	
Grade I-III	5 (71)
Grade IV-V	2 (29)
Admission GCS, median (IQR)	14 (2)
APACHE, mean ± SD	2 ± 3
APACHE sub score, mean ± SD	8 ± 3
FT, n (%)	3 (43)
Tablet form, n (%)	4 (57)

ACOMM, anterior communicating artery; APACHE, Acute Physiology and Chronic Healthy Evaluation; BMI, body mass index; FT, patients who took nimodipine by feeding tube (crushed); GCS, Glasgow Coma Scale; MCA, middle cerebral artery; PCOM, posterior communicating artery; WFNS, World Federation of Neurological Surgeons.

4.4.2 Plasma Nimodipine Enantiomer Concentrations

A total of 35 blood samples were collected, 15 of which were from patients who received nimodipine by enteral feeding tubes. The median (IQR) $AUC_{0\text{-}4h}$, C_{max}, T_{max} and the trough of each patient are depicted in **Tables 4-4 and 4-5**. The median (IQR) $AUC_{0\text{-}4h}$ was)16.1 (12.8) for (-)-S enantiomer and 39.9 (49.8) ng*h/ml for the (+)-R enantiomer whereas the median (IQR) of C_{max} for (-)-S- and (+)-R-nimodipine were 5 (5) and 19.3 (13) ng/ml, respectively. The median (IQR) T_{max} for both enantiomers were 0.52 (0.4) hour. (**Figure 4-1**, **4-2)** represents the AUC curves for nimodipine enantiomers in the 7 patients.

Table 4-4: Pharmacokinetics of S-nimodipine in SAH patients

Patient number	AUC_{0-4h} (ng*h/ml)	C_{max} (ng/ml)	T_{max} (h)	Trough (0 h) (ng/ml)	CL/F (L/h/kg)	Vdss/F (L/kg)
1	19.9	10.3	0.65	4.3	32.3	54.6
2	79.6	40.2	0.34	14.8	7.2	12.0
3	19.6	5.3	1.47	4.8	30.6	60.0
4	6.5	1.7	1.05	1.6	113.2	229.8
5	16.1	5	0.5	3.5	53.3	102.0
6	7.4	3.6	0.52	1.3	63.3	106.2
7	3	1.1	0.5	0.5	387.4	726.4
Median (IQR)	16.1(12.8)	5 (5)	0.52 (0.4)	3.5 (3)	53.3(56.8)	102(110.7)

AUC, area under plasma drug concentration-time curve; C_{max}, maximum (or peak) serum concentration; CL/F, oral clearance; T_{max}, time at which C_{max} is attained; Vdss/F, apparent volume of distribution at steady state.

Table 4-5: Pharmacokinetics of R-nimodipine in SAH patients

Patient number	AUC_{0-4h} (ng*h/ml)	C_{max} (ng/ml)	T_{max} (h)	Trough (0 h) (ng/ml)	CL/F (L/h/kg)	Vdss/F (L/kg)
1	86.3	30	0.65	20	7.5	13.9
2	315.7	117.6	0.34	66.8	1.8	3.3
3	31.1	10.8	0.47	6.8	19.3	35.4
4	29.7	8.5	1.05	6.7	24.9	50.1
5	74.1	24	0.5	15	11.6	22.3
6	39.9	16.6	0.52	7.3	11.8	20.9
7	22.2	19.3	1.5	1.1	51.9	82.2
Median (IQR)	39.9 (49.8)	19.3 (13)	0.52 (0.4)	7.3 (11)	11.8(12.55)	22.3(25.35)

AUC, area under plasma drug concentration-time curve; C_{max}, maximum (or peak) serum concentration; CL/F, oral clearance; T_{max}, time at which C_{max} is attained; Vdss/F, apparent volume of distribution at steady state.

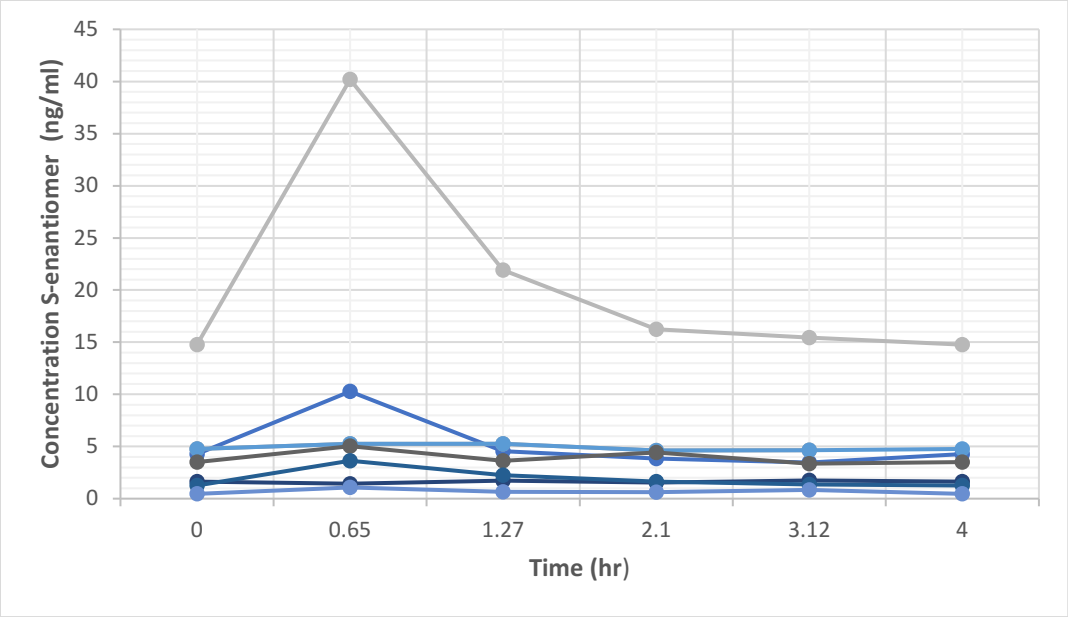

Figure 4-1: Time vs. (-)-S nimodipine plasma concentration curves for the patients included in the study (n=7).

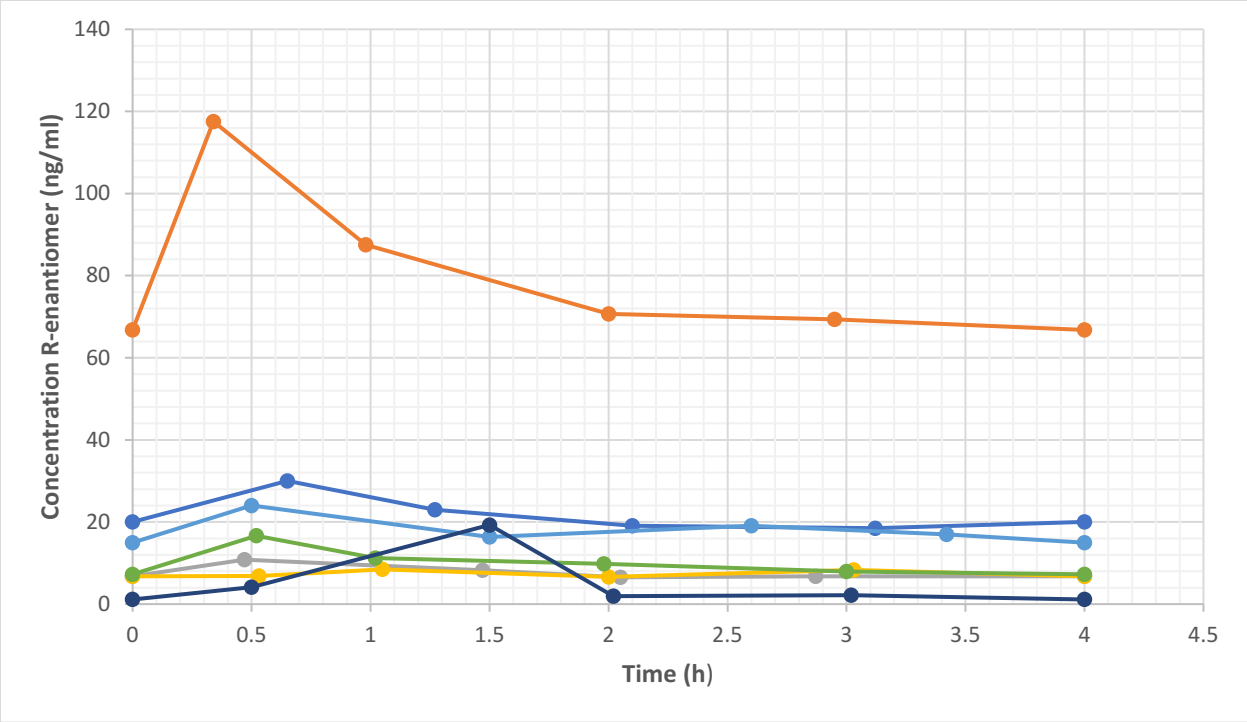

Figure 4-2: Time vs. (+)-R nimodipine plasma concentration curves for the patients included in the study (n=7).

4.4.3 The Effect of Route of Administration on Nimodipine Exposure

Among the 7 patients in the study, 3 patients had taken nimodipine as crushed tablets washed down through the nasogastric tube and 4 received nimodipine orally as whole tablets. There was a trend in FT patients having a lower median $AUC_{0\text{-}4h}$ value compared to the patients who got nimodipine as tablet [6.5 (2.2) and 29.7 (8.9)] for -(-) S and-(+)-R nimodipine, respectively vs [19.8 (16.1) and 80.2 (80.3) for - (-)-S and-(+)-R nimodipine, respectively), as shown in **Figure 4-3**. The lowest $AUC_{0\text{-}4h}$ was recorded as low as 3 ng*h/ml for (-)-S nimodipine with a patient who had taken nimodipine through FT. The highest median $AUC_{0\text{-}4h}$ of all patients has been seen for a patient in the oral group (79.6 and 315.7 ng*h/ml, for (-)-S and (+)-R nimodipine, respectively)**.**

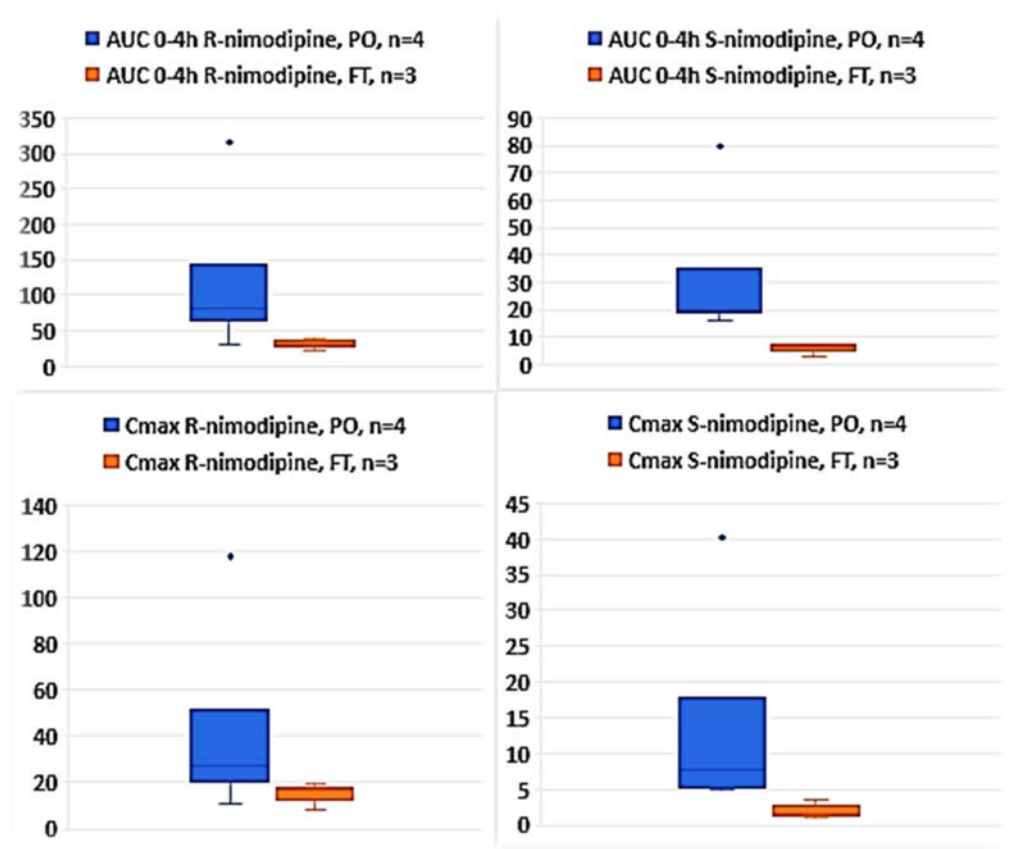

Figure 4-3: $AUC_{0\text{-}4h}$ of nimodipine (±) and C_{max} of tablet vs feeding tube administration.

AUC, area under plasma drug concentration-time -curve; C-max, maximum (or peak) serum concentration; FT, patients who took nimodipine by feeding tube (crushed); PO, patients who took nimodipine by tablet form.

4.4.4 The Effect of Age on Nimodipine Exposure

There was a non-significant trend of higher nimodipine exposure in older subjects (age > 70 years) compared to young ones. The median (IQR) $AUC_{0\text{-}4h}$ of those older than 70 years (n=2) were 181.9) ng*h/ml and 80.2(6.1 for (-)-S and (+)-R enantiomers, respectively while for those younger than 70 years (n=5) had $AUC_{0\text{-}4h}$ of 7.4 (13.1) ng*h/ml and 31.1(10.2) for (-)-S and (+)-R nimodipine, respectively, as depicted in **Figure 4-4**

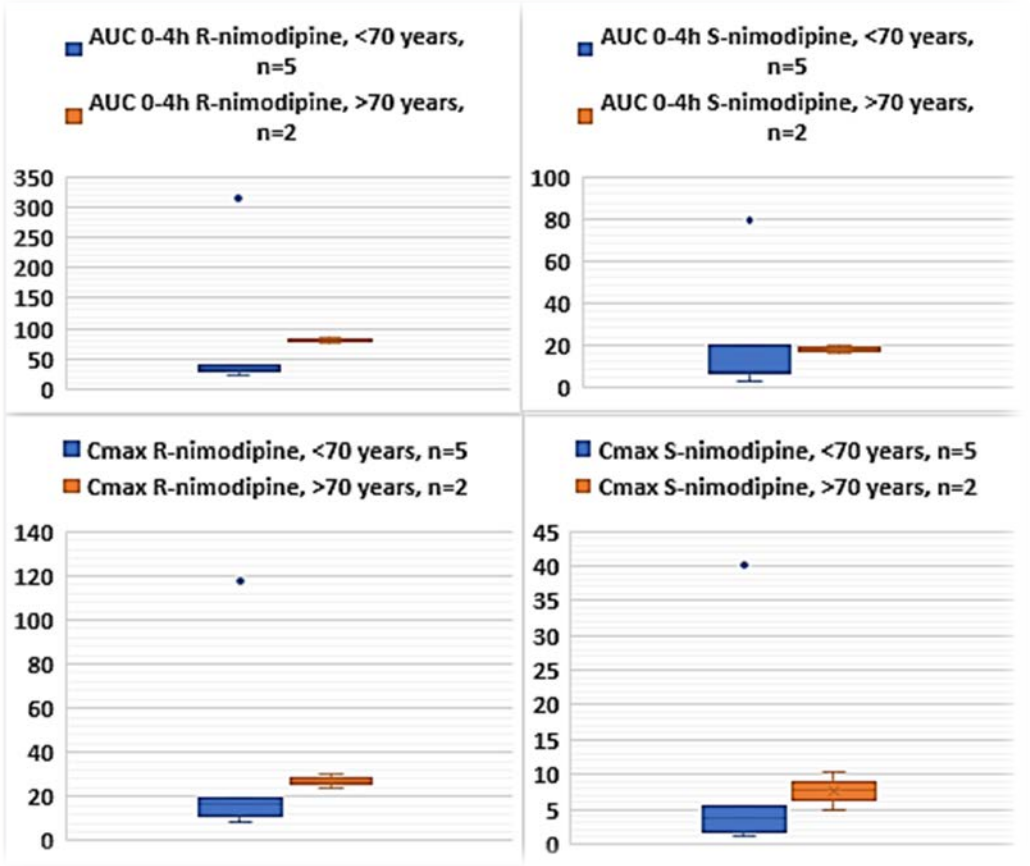

Figure 4-4: $AUC_{0\text{-}4h}$ of nimodipine (±) and C_{max} of young (<70) years vs elder (>70) years.

AUC, area under plasma drug concentration-time -curve; C-max, maximum (or peak) serum concentration.

4.4.5 The Effect Disease Severity (WFNS) on Nimodipine Exposure

Only two patients were high Grade WFNS (IV-V) and 5 were good Grade (I-III). High Grade patients had non significantly lower median $AUC_{0\text{-}4h}$ (IQR) than the good grade ones [11.3 (8.3) ng*h/ml vs 16.1(12.5) ng*h/ml, respectively] for S- and [26.65 (4.5) ng*h/ml vs 74.1 (46.4) ng*h/ml, respectively] for R-nimodipine, **Figure 4-5.**

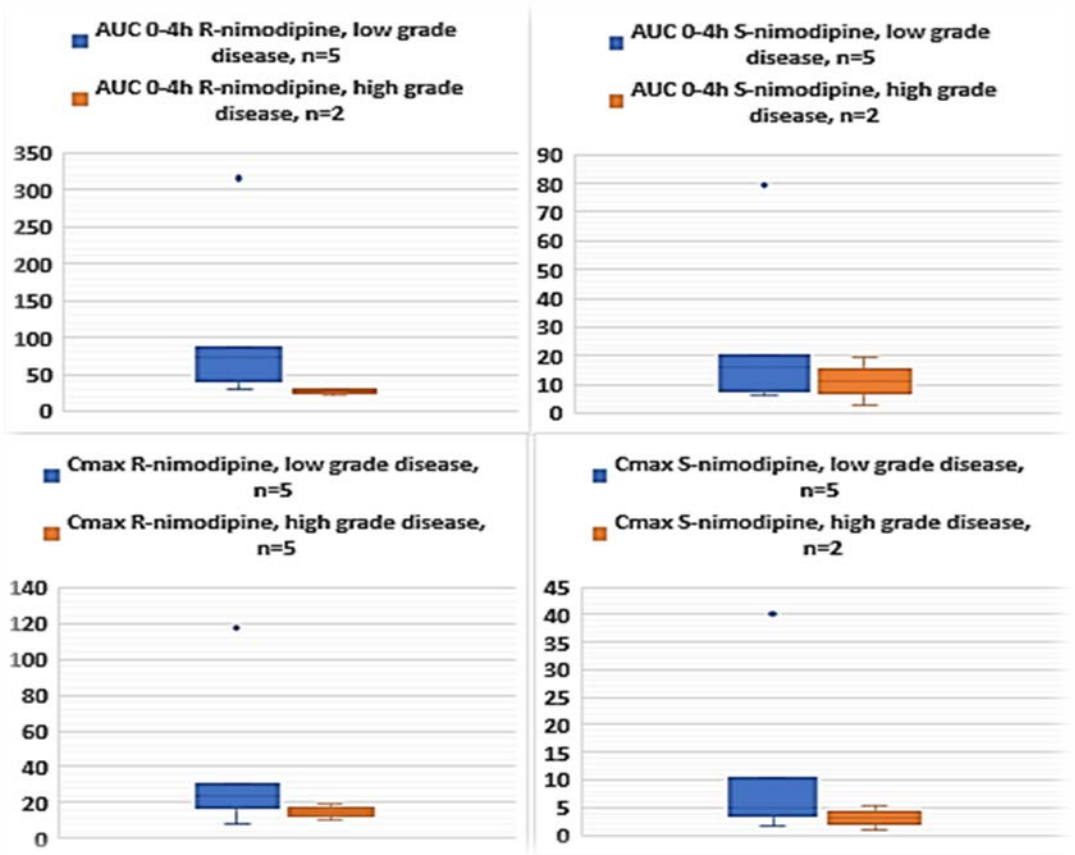

Figure 4-5: $AUC_{0\text{-}4h}$ of nimodipine (±) and C_{max} of low-grade disease vs high grade disease.

AUC, area under plasma drug concentration-time -curve; C-max, maximum (or peak) serum concentration

4.4.6 Nimodipine Exposure and Clinical Outcomes

4.4.6.1 Discharge Outcomes

Two patients developed vasospasm during the hospital stay. Comparing the median (IQR) AUC_{0-4h} of these two patients with those who did not develop vasospasm, there was a trend towards non significantly lower exposure in the two patients [13.5(6.1) versus 16.1 (13.4) ng*h/ml] for (-)-S and [35.5 (.4) versus 74.1 (56.6) ng*h/ml] for (+)-R nimodipine, as presented in **Figure 4-6**. Only one patient suffered from DCI and died in the hospital. The AUC_{0-4h} measurement of the patients who died was 16.1 ng*h/ml and 74.1 ng*h/ml for (-)-S and (+)-R isomers, respectively which is comparable to AUC_{0-4h} for all patients**.** The patients were discharged to either home or continuing care facilities. Apart from the patient who had died, 4 patients were discharged to home and 2 patients were transferred to continuing care centres. The 2 patients who had been transferred to care facilities had lower median (IQR) AUC_{0-4h} of (+)-R nimodipine compared to those discharged home [35.5 (4.4) versus (58 (115.8) ng*h/ml].

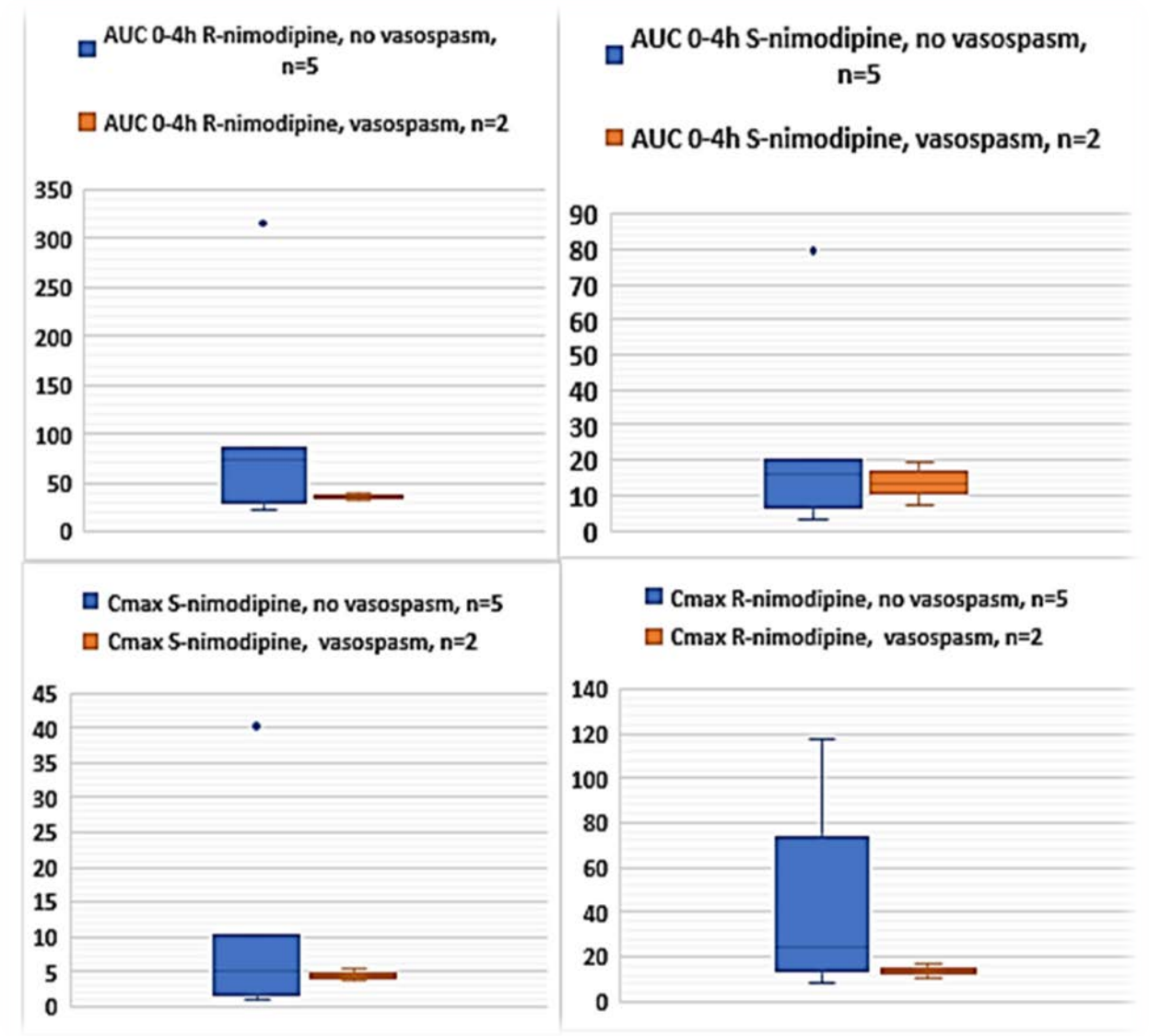

Figure 4-6: $AUC_{0\text{-}4h}$ of nimodipine (±) and C_{max} of patients with vasospasm vs no vasospasm.

AUC, area under plasma drug concentration-time -curve; C-max, maximum (or peak) serum concentration

4.4.6.2 Three Months Modified Rankin Scale for Neurologic Disability Outcome

Among the seven patients in this pilot study, the 3 months mRS scores were assigned as follow: two patients had their disabilities scored as 1, four patients as score 3, and one patient had fallen into Score 6. Analyzing the nimodipine exposure variations among different scores, we found out that the median (IQR) of AUC $_{0\text{-}4h}$ values of (+)-R nimodipine were non significantly less in patients assigned as score 3 than those with Score one [35.5 (80.0) versus 58 (28.3) ng*h/ml, respectively]

4.5 Discussion

The findings of this pilot study have shown a wide interindividual variation in the pharmacokinetics of orally administered nimodipine in SAH. As reported by other studies, plasma nimodipine concentrations are variable and there is no established reference range for of nimodipine. The reported $AUC_{0\text{-}4h}$ and C_{max} values in this pilot for (-)-S and (+)-R enantiomer were similar to the ranges reported, previously.(242, 248, 260) Also, the T_{max} found in agreement of the reported T_{max} in the literature (174, 175). The difference of (-)-S and (+)-R nimodipine plasma levels supports the phenomenon of the enantioselective metabolism and the higher hepatic clearance of (-)-S than (+)-R- enantiomer (187). As discussed in the nimodipine section in **CHAPTER 1**, the inter-individual nimodipine plasma variation could be attributed to multiple factors such as the administration technique (e.g. FT versus tablet form administration), age, and disease severity. Although the sample size of this pilot study is not sufficient to detect difference in plasma drug exposure between various patient categories, there was a trend of lower plasma nimodipine levels with FT administration as shown in one patient who was administered nimodipine through NG and found to have the lowest $AUC_{0\text{-}4h}$ value amongst all the seven patients.

This is similar to what has been previously reported by studies (190, 198, 241). In addition, age plays role in nimodipine exposure as older adults have reduced hepatic clearance of the racemic drug and in turn higher AUC and Cmax than the youngsters (223). The findings of this pilot study also found this difference regarding $AUC_{0\text{-}4h}$ and $C\text{-}_{max}$ of nimodipine between the elder and non-elder populations. Moreover, patients presented with severe illness (i.e., high grade SAH, WFNS > III) always tend to have altered mental status and most likely to receive nimodipine through NG. The findings of this pilot study have shown that the high-grade patients had less nimodipine exposure than the good grade patients. The reason behind this lower plasma levels could probably be the FT administration (190, 198, 241) or perhaps the severity of the disease that can predispose the patients to gastrointestinal malfunction (260). Further, studies are needed to confirm such finding.

The most clinically important question is whether the inter-individual orally dosed nimodipine plasma variation affects patient outcomes. The answer to this question remains unknown; however, this pilot study investigated the discharge outcomes and the 3-month outcomes in patients who were treated with oral nimodipine. This pilot study preliminarily determined that the median $AUC_{0\text{-}4h}$ values for two nimodipine enantiomers were lower in 2 patients who had developed vasospasm. In addition to this, there was lower $AUC_{0\text{-}4h}$ of (+)-R-nimodipine in patients who were transferred to continuing care facilities. There was also a lower trend of (+)-R nimodipine exposure for patients who had mRS score of 3 than those who scored 1. Previous retrospective chart review study carried out by our team has found that there was an association between FT administration and the likelihood of poor outcome in SAH patients (261). This was a pilot study with only seven patients involved, and we can only draw a few preliminary inferences. The clinical relevance of the findings of this study warrants further investigations with larger sample size design.

4.6 Conclusion

This pilot study indicated preliminary findings of nimodipine interindividual variations with possible factors that could contribute to those alterations in serum drug levels and possibly lower exposure trend with poorer outcomes. This is a pilot study with no means to perform statistically meaningful comparisons; the findings need further confirmatory prospective studies with larger sample size to investigate the effect of the inter-individual orally dosed nimodipine pharmacokinetic variations on patient outcomes.

References

2. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365-72.

8. Diringer MN, Bleck TP, Claude Hemphill J, 3rd, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15(2):211-40.

92. Kassell NF, Torner JC, Haley EC, Jr., Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg. 1990;73(1):18-36.

102. Geraghty JR, Testai FD. Delayed Cerebral Ischemia after Subarachnoid Hemorrhage: Beyond Vasospasm and Towards a Multifactorial Pathophysiology. Curr Atheroscler Rep. 2017;19(12):50.

103. Rowland MJ, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. Br J Anaesth. 2012;109(3):315-29.

104. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke. 2010;41(10):2391-5.

148. Lopez-Arrieta JM, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. Cochrane Database Syst Rev. 2002(3):Cd000147.

149. Wessell A, Kole MJ, Badjatia N, Parikh G, Albrecht JS, Schreibman DL, et al. High Compliance with Scheduled Nimodipine Is Associated with Better Outcome in Aneurysmal Subarachnoid Hemorrhage Patients Cotreated with Heparin Infusion. Front Neurol. 2017;8:268.

156. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg. 1988;68(4):505-17.

157. Philippon J, Grob R, Dagreou F, Guggiari M, Rivierez M, Viars P. Acta Neurochir (Wien) (1986) 82:110-114 eCt ahirurgica Prevention of Vasospasm in Subarachnoid Haemorrhage. A Controlled Study with Nimodipine. 1986:110-4.

158. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989;298(6674):636-42.

159. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, et al. Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308(11):619-24.

174. Langley MS, Sorkin EM. Nimodipine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs. 1989;37(5):669-99.

175. Muck W, Ahr G, Kuhlmann J. Nimodipine. Potential for drug-drug interactions in the elderly. Drugs & aging. 1995;6(3):229-42.

187. Wanner-Olsen H, Gaarskaer FB, Mikkelsen EO, Jakobsen P, Voldby B. Studies on concentration-time profiles of nimodipine enantiomers following intravenous and oral

administration of nimodipine in patients with subarachnoid hemorrhage. Chirality. 2000;12(9):660-4.
190. Abboud T, Andresen H, Koeppen J, Czorlich P, Duehrsen L, Stenzig J, et al. Serum levels of nimodipine in enteral and parenteral administration in patients with aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien). 2015;157(5):763-7.
194. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European Journal of Clinical Pharmacology. 1993;45(4):363-6.
198. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage – a pilot study. European Journal of Clinical Pharmacology. 2007;63:355-61.
200. Vinge E, Andersson KE, Brandt L. Pharmacokinetics of nimodipine in patients with aneurysmal subarachnoid haemorrhage. European Journal of Clinical Pharmacology. 1986;30(4):421-5.
210. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, et al. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. British Journal Of Clinical Pharmacology. 1991;32(3):335-40.
223. Eicher H, Hilgert D, Zeeh J, Platt D, Becker C, Mutschler E. Pharmacokinetics of nimodipine in multimorbid elderly patients with chronic brain failure. Arch Gerontol Geriatr. 1992;14(3):309-19.
225. Albanna W, Weiss M, Conzen C, Clusmann H, Schneider T, Reinsch M, et al. Systemic and Cerebral Concentration of Nimodipine During Established and Experimental Vasospasm Treatment. World Neurosurg. 2017.
236. Schmith VD, Foss JF. Effects of inflammation on pharmacokinetics/pharmacodynamics: increasing recognition of its contribution to variability in response. Clin Pharmacol Ther. 2008;83(6):809-11.
237. 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):238-42.
241. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European journal of clinical pharmacology. 1993;45(4):363-6.
242. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. Eur J Clin Pharmacol. 1993;45(4):363-6.
248. Abboud T, Andresen H, Koeppen J, Czorlich P, Duehrsen L, Stenzig J, et al. Serum levels of nimodipine in enteral and parenteral administration in patients with aneurysmal subarachnoid hemorrhage. Acta Neurochirurgica. 2015;157(5):763-7.
259. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604-7.
260. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage-a pilot study.
261. Isse FA, Abdallah YEH, Mahmoud SH. The Impact of Nimodipine Administration through Feeding Tube on Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage. J Pharm Pharm Sci. 2020;23(1):100-8.

Chapter 5 Discussion

Aneurysmal SAH is life-threatening neurological condition that affects relatively young age leading to premature loss of a productive life years. Initial survivors of SAH tend to face post SAH complications where some of those complications can put patient's life at risk of death or cause permanent loss of functional and productive life (2). Vasospasm is one of the major complications that leads to unfavourable clinical outcome. Nimodipine is the only pharmacologic intervention to prevent those complication by improving patient's neurological outcomes (156-159). Randomized clinical trials of oral nimodipine therapy in patients with subarachnoid haemorrhage (156-159) clearly confirmed the drug's benefit in improving patients' functional outcomes by reducing the incidence of neurologic deficits. Despite this solid evidence of favourable outcome with nimodipine, in each trial, there were some patients who did not get the supposed protective action of nimodipine (up to 22%) (156, 158, 159). In addition, to this, poor grade patients did not get the benefit of nimodipine. The dose of nimodipine is empiric and based on previous RCTs doses (Philippon et al.1986 and Pickard et al.1989 used 60mg q4h while Petruck et al.1988 used 90mg Q4h; Allen et al.1983 used 0.35mg/kg Q4h). A comprehensive review of literature carried out by our team revealed an extensive inter-individual variation in oral nimodipine pharmacokinetics. The observed variability may have been attributed to practice variations in nimodipine administration, disease severity, administration of concomitant interacting drugs and cytochrome P450 polymorphism, liver dysfunction and age. To start with the administration technique, which is varied in practice, nimodipine is administered as a whole tablet if patients can swallow the whole tablet otherwise tablets are crushed and washed down through nasogastric tube. Also, sick patients who are unable to swallow the capsule, the content of the capsule is drawn and given through nasogastric tube. Only tablet formulation is available in Canada, leaving the sick patients to be treated with crushed nimodipine tablets administered through FT. Most of previous nimodipine

pharmacokinetic studies if not all, reported low plasma levels of the drug following FT administration (198, 241, 248). Abboud et al have conducted a pharmacokinetic study on nimodipine enteral administration in SAH patients. In patients who were unable to swallow, the tablets were crushed and administered through nasogastric tubes. They have reported that nimodipine exposure as measured by the area under the concentration-time curve (AUC) in the FT group was lower than those who swallowed the whole tablets (median AUC 23.1 vs. 52.3 ng.h/ml, respectively, *p* value 0.006). In addition, two high grade patients had undetectable plasma levels of nimodipine (248). Similarly, Kumana et al. have reported reduced bioavailability of nimodipine in a patient given crushed tablets through gastric tube (241). Also, Soppi et al have reported lower plasma levels of nimodipine in 3 patients with high grade SAH who were given nimodipine extemporaneously prepared suspension through nasogastric tube. Disease severity is another patient-specific factor that can have an influence on nimodipine plasma levels (190, 194, 225, 229). In general, poor grade patients had significantly lower C_{max} and AUC values than those observed in good-grade patients. This suggests that the observed differential effects of SAH grade could be attributed to reduced nimodipine bioavailability secondary to administration via feeding tube rather than altered drug clearance. Concomitant interacting drug is also a source of variation where enzyme inducers contribute to lower plasma nimodipine concentration (229) opposing the effect of enzyme inhibitors where nimodipine plasma level elevation occur (210) . Cytochrome P450 polymorphism has been also reported to be part of the nimodipine PK variation affecting on nimodipine clearance. Patients with homozygous version of CYP3A5 (*3/*3) have decreased plasma nimodipine clearance (212). Since hepatic metabolism is the main route of nimodipine elimination, the influence of liver cirrhosis on nimodipine PK seem to be apparent. Oral clearance of nimodipine is substantially lower in liver cirrhosis patients than in healthy subjects (203).

Besides to hepatic dysfunction, factors that can alter hepatic clearance such as age also contribute to higher plasma levels of nimodipine (214, 222). With the knowledge of above -mentioned factors that impact nimodipine plasma levels particularly the lower exposure reported with the FT nimodipine administration, here comes the most important question of whether the reduced systemic exposure of nimodipine changes its therapeutic benefit in patients with aneurysmal SAH. This question remained unanswered in the literature. For that reason, our team conducted a retrospective chart review study which investigated whether taking nimodipine through FT has an impact on clinical outcomes in the first 7 days and over 21 days of patient admission. After adjusting for disease severity and other covariates, nimodipine administration technique was associated with vasospasm in the first 7 days of patient admission where patients receiving nimodipine via FT had increased odds of angiographic vasospasm compared to those administered it as whole tablets (OR 8.9, 95% CI 1.1-73.1, *p* value 0.042). In addition, nimodipine administration by feeding tube over the 21-days period was independently associated with DCI (OR 38.1 compared to those receiving whole tablets, 95% CI 1.4-1067.9, *p* value 0.032) (261). Although this was a retrospective chart review study with its own limitations, it suggested that administration of nimodipine through this mode could result poor outcomes. This is probably due to reduced bioavailability of nimodipine following the FT administration. However, it is not clear if the observed reduced bioavailability is a function of the formulation itself, altered pharmacokinetics in SAH patients with high disease severity or both. Reduced bioavailability of drugs secondary to gastrointestinal dysfunction in critically ill patients and those in pain has been reported previously (253, 254).

Nimodipine is a chiral compound with an asymmetric carbon at position 4 of the dihydropyridine ring structure and it is marketed as a racemic mixture of (+)-R and (-)-S enantiomers. Towart et al

have found that (-)-S nimodipine is approximately twice as potent vasorelaxant as the racemic mixture (169). In addition, the (-)-S enantiomer is more rapidly eliminated than (+)-R counterpart following oral dosing resulting in significantly lower (-)-S enantiomer concentrations (184, 187, 245). The clinical relevance of this differential clearance is unknown. Most of the nimodipine assays available in literature are non-enantioselective. Three methods have reported enantioselective assay for nimodipine (184, 187, 245). However, the reported methods were time-consuming, involved multi-step extraction procedures and required large sample volumes. We developed sensitive, selective, enantioselective method for nimodipine which involve one step liquid-liquid extraction and used a smaller volume of human plasma (300µl). High quality separation of the two peaks of nimodipine enantiomers was achieved by using a chiral stationary phase column with methanol- water (75:25) eluent. The current nimodipine assay covers the range of 1.5-75 ng/ml for each enantiomer. The extraction recovery was sufficient to analyze nimodipine enantiomer concentrations with reasonable accuracy and precision. The application of the method was performed in the analysis of plasma concentrations obtained from an aneurysmal subarachnoid hemorrhage patient enrolled in a prospective nimodipine pharmacokinetic and outcome study (a pilot study). The pilot study was deigned to provide us a preliminary data about nimodipine interindividual pharmacokinetic variations among different patient categories. Also, to study if there is any trend of having lower exposure with different outcome classifications. The preliminary finding showed variation in nimodipine plasma levels among the seven patients enrolled. The $AUC_{0\text{-}4h}$ of nimodipine ranged from 2.5ng*h/ml to 20.6 ng*h/ml for (-)-S and from 63.7 ng*h/ml to 244.2 ng*h/ml for (+)-R nimodipine. The $AUC_{0\text{-}4h}$ of (-)-S was lower than (+)-R nimodipine due to enantioselective metabolism by liver. This phenomenon has been previously reported by studies (184, 187, 245). Subgroup analysis revealed a trend towards lower exposure with FT

nimodipine administration. This lower nimodipine exposure with the feeding tube administration has been previously reported by studies (190, 198, 241). Moreover, Patients who their disease graded as high (WFNS > III) always tend to be unconscious and most likely to receive nimodipine through NG. The findings of this pilot study have shown that the high-grade patients had less nimodipine exposure than the good grade patients which is keeping with previous reports of linked lower nimodipine plasma levels to high grade patients (190, 194, 225, 229). The most clinically important question is whether the inter-individual orally dosed nimodipine plasma variation affects patient outcomes. This pilot study preliminarily determined that the median $AUC_{0\text{-}4h}$ values for two nimodipine enantiomers were lower in 2 patients who had developed vasospasm. In addition to this, there was lower $AUC_{0\text{-}4h}$ of (+)-R-nimodipine in patients who were transferred to continuing care facilities. There was also a lower trend of (+)-R nimodipine exposure for patients who had modified Rankin Scale of 3 than Scale 1. This was a pilot study with only seven patients involved, and we can only draw a few preliminary inferences. The clinical relevance of the findings of this study warrants further investigations with larger sample size design. However, these pilot findings indicate the factors that can possibly influence the plasma nimodipine levels and a trend towards lower drug plasma exposure in poorer outcomes.

5.1 Future Directions

This research highlighted the need for further outcome investigation in poor grade patients who receive nimodipine through FT as those patients were reported to have lower nimodipine plasma levels or sometimes negligible serum drug levels. Our retrospective study findings direct the need for future multicentre retrospective study that involves investigating the FT administration and its impact on the clinical outcomes in patients with SAH. Also, an in vitro study examining the absorption of crushed tablets and administering them through feeding tube is needed to know whether the problem is from reduced absorption due to incomplete dissolution of tablets or binding the drug to the tubes or from altered PK in sick patients with SAH. The literature review data revealed inter-individual nimodipine variation among patient groups and the potential sources of the variation which raised a concern about fixed dose nimodipine regimen and shapes the future towards an individualized dosing approach by taking all these patient-specific and non-patient specific factors into consideration and hence individualized nimodipine pharmacotherapy in SAH patients. The pilot study's preliminary results will lay the foundation for a future prospective pharmacokinetic and outcome study to investigate the association between nimodipine exposure and patient outcomes.

References

2. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365-72.

156. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg. 1988;68(4):505-17.

157. Philippon J, Grob R, Dagreou F, Guggiari M, Rivierez M, Viars P. Acta Neurochir (Wien) (1986) 82:110-114 eCt ahirurgica Prevention of Vasospasm in Subarachnoid Haemorrhage. A Controlled Study with Nimodipine. 1986:110-4.

158. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989;298(6674):636-42.

159. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, et al. Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308(11):619-24.

169. R.Towart EW, H.Meyer, and S.Kazda. The Effect of Nimodipine, its Optical Isomers and Metabolites on Isolated Vascular Smooth Muscle. ArzneimForsch/Drug Res. 1982;32(1):338-46.

184. Fischer C, Schonberger F, Muck W, Heuck K, Eichelbaum M. Simultaneous assessment of the intravenous and oral disposition of the enantiomers of racemic nimodipine by chiral stationary-phase high-performance liquid chromatography and gas chromatography/mass spectroscopy combined with a stable isotope technique. J Pharm Sci. 1993;82(3):244-50.

187. Wanner-Olsen H, Gaarskaer FB, Mikkelsen EO, Jakobsen P, Voldby B. Studies on concentration-time profiles of nimodipine enantiomers following intravenous and oral administration of nimodipine in patients with subarachnoid hemorrhage. Chirality. 2000;12(9):660-4.

190. Abboud T, Andresen H, Koeppen J, Czorlich P, Duehrsen L, Stenzig J, et al. Serum levels of nimodipine in enteral and parenteral administration in patients with aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien). 2015;157(5):763-7.

194. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European Journal of Clinical Pharmacology. 1993;45(4):363-6.

198. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage – a pilot study. European Journal of Clinical Pharmacology. 2007;63:355-61.

203. Gengo FM, Fagan SC, Krol G, Bernhard H. Nimodipine disposition and haemodynamic effects in patients with cirrhosis and age-matched controls. British Journal of Clinical Pharmacology. 1987;23(1):47-53.

210. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, et al. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. British Journal Of Clinical Pharmacology. 1991;32(3):335-40.

212. 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. European Journal Of Clinical Pharmacology. 2009;65(6):579-84.

214. Eicher H, Hilgert D, Zeeh J, Platt D, Becker C, Mutschler E. Pharmacokinetics of nimodipine in multimorbid elderly patients with chronic brain failure. Archives of Gerontology and Geriatrics. 1992;14(3):309-19.
222. W.Muck HPB, J.Kuhlmann. The influence of age on pharmacokinetics of nimodipine*. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(7):293-8.
225. Albanna W, Weiss M, Conzen C, Clusmann H, Schneider T, Reinsch M, et al. Systemic and Cerebral Concentration of Nimodipine During Established and Experimental Vasospasm Treatment. World Neurosurg. 2017.
229. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage - a pilot study. European Journal Of Clinical Pharmacology. 2007;63(4):355-61.
241. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European journal of clinical pharmacology. 1993;45(4):363-6.
245. Muck WM. Enantiospecific determination of nimodipine in human plasma by liquid chromatography-tandem mass spectrometry. Journal of Chromatography A. 1995;712(1):45-53.
248. Abboud T, Andresen H, Koeppen J, Czorlich P, Duehrsen L, Stenzig J, et al. Serum levels of nimodipine in enteral and parenteral administration in patients with aneurysmal subarachnoid hemorrhage. Acta Neurochirurgica. 2015;157(5):763-7.
253. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin. 2006;22(2):255-71, vi.
254. Jamali F, Kunz-Dober CM. Pain-mediated altered absorption and metabolism of ibuprofen: an explanation for decreased serum enantiomer concentration after dental surgery. Br J Clin Pharmacol. 1999;47(4):391-6.
261. Isse FA, Abdallah YEH, Mahmoud SH. The Impact of Nimodipine Administration through Feeding Tube on Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage. J Pharm Pharm Sci. 2020;23(1):100-8.

Chapter 6 References

1. Gasparotti R, Liserre R. Intracranial aneurysms. Eur Radiol. 2005;15(3):441-7.
2. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365-72.
3. . !!! INVALID CITATION !!! (3).
4. Huang YH, Liao CC, Yang KY. Demographics and Short-Term Outcomes of Spontaneous Subarachnoid Hemorrhage in Young Adults. World Neurosurg. 2017;102:414-9.
5. Ogungbo B, Gregson B, Blackburn A, Barnes J, Vivar R, Sengupta R, et al. Aneurysmal subarachnoid hemorrhage in young adults. J Neurosurg. 2003;98(1):43-9.
6. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012;43(6):1711-37.
7. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354(4):387-96.
8. Diringer MN, Bleck TP, Claude Hemphill J, 3rd, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15(2):211-40.
9. Roos YB, Dijkgraaf MG, Albrecht KW, Beenen LF, Groen RJ, de Haan RJ, et al. Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. Stroke. 2002;33(6):1595-9.
10. Marcolini E, Hine J. Approach to the Diagnosis and Management of Subarachnoid Hemorrhage. West J Emerg Med. 2019;20(2):203-11.
11. Jakubowski J, Kendall B. Coincidental aneurysms with tumours of pituitary origin. J Neurol Neurosurg Psychiatry. 1978;41(11):972-9.
12. Brown RD, Jr., Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. Lancet Neurol. 2014;13(4):393-404.
13. Williams LN, Brown RD, Jr. Management of unruptured intracranial aneurysms. Neurol Clin Pract. 2013;3(2):99-108.
14. Bor AS, Koffijberg H, Wermer MJ, Rinkel GJ. Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis. Neurology. 2010;74(21):1671-9.
15. Broderick JP, Brown RD, Jr., Sauerbeck L, Hornung R, Huston J, 3rd, Woo D, et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. Stroke. 2009;40(6):1952-7.
16. Schievink WI, Michels VV, Piepgras DG. Neurovascular manifestations of heritable connective tissue disorders. A review. Stroke. 1994;25(4):889-903.
17. Broderick JP, Viscoli CM, Brott T, Kernan WN, Brass LM, Feldmann E, et al. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. Stroke. 2003;34(6):1375-81.
18. Broderick JP, Brott T, Tomsick T, Huster G, Miller R. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. N Engl J Med. 1992;326(11):733-6.

19. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke. 2005;36(12):2773-80.
20. Edlow JA, Panagos PD, Godwin SA, Thomas TL, Decker WW, American College of Emergency P, et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. Ann Emerg Med. 2008;52(4):407-36.
21. Bassi P, Bandera R, Loiero M, Tognoni G, Mangoni A. Warning signs in subarachnoid hemorrhage: a cooperative study. Acta Neurol Scand. 1991;84(4):277-81.
22. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. Cephalalgia. 2003;23(10):935-41.
23. Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. Neurosurg Focus. 2009;26(5):E2.
24. Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103-10.
25. Kowalski RG, Claassen J, Kreiter KT, Bates JE, Ostapkovich ND, Connolly ES, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. Jama. 2004;291(7):866-9.
26. Meurer WJ, Walsh B, Vilke GM, Coyne CJ. Clinical Guidelines for the Emergency Department Evaluation of Subarachnoid Hemorrhage. J Emerg Med. 2016;50(4):696-701.
27. Panczykowski D, Pease M, Zhao Y, Weiner G, Ares W, Crago E, et al. Prophylactic Antiepileptics and Seizure Incidence Following Subarachnoid Hemorrhage: A Propensity Score-Matched Analysis. Stroke. 2016;47(7):1754-60.
28. Sames TA, Storrow AB, Finkelstein JA, Magoon MR. Sensitivity of new-generation computed tomography in subarachnoid hemorrhage. Acad Emerg Med. 1996;3(1):16-20.
29. van der Jagt M, Hasan D, Bijvoet HW, Pieterman H, Dippel DW, Vermeij FH, et al. Validity of prediction of the site of ruptured intracranial aneurysms with CT. Neurology. 1999;52(1):34-9.
30. Agid R, Andersson T, Almqvist H, Willinsky RA, Lee SK, terBrugge KG, et al. Negative CT angiography findings in patients with spontaneous subarachnoid hemorrhage: When is digital subtraction angiography still needed? AJNR Am J Neuroradiol. 2010;31(4):696-705.
31. Sayer D, Bloom B, Fernando K, Jones S, Benton S, Dev S, et al. An Observational Study of 2,248 Patients Presenting With Headache, Suggestive of Subarachnoid Hemorrhage, Who Received Lumbar Punctures Following Normal Computed Tomography of the Head. Acad Emerg Med. 2015;22(11):1267-73.
32. Kuntz KM, Kokmen E, Stevens JC, Miller P, Offord KP, Ho MM. Post-lumbar puncture headaches: experience in 501 consecutive procedures. Neurology. 1992;42(10):1884-7.
33. Fox AJ, Symons SP, Aviv RI. CT angiography is state-of-the-art first vascular imaging for subarachnoid hemorrhage. AJNR Am J Neuroradiol. 2008;29(6):e41-2; author reply e6-7.
34. Prestigiacomo CJ, Sabit A, He W, Jethwa P, Gandhi C, Russin J. Three dimensional CT angiography versus digital subtraction angiography in the detection of intracranial aneurysms in subarachnoid hemorrhage. J Neurointerv Surg. 2010;2(4):385-9.
35. Kershenovich A, Rappaport ZH, Maimon S. Brain computed tomography angiographic scans as the sole diagnostic examination for excluding aneurysms in patients with perimesencephalic subarachnoid hemorrhage. Neurosurgery. 2006;59(4):798-801; discussion -2.

36. Luo Z, Wang D, Sun X, Zhang T, Liu F, Dong D, et al. Comparison of the accuracy of subtraction CT angiography performed on 320-detector row volume CT with conventional CT angiography for diagnosis of intracranial aneurysms. Eur J Radiol. 2012;81(1):118-22.
37. Yeung R, Ahmad T, Aviv RI, de Tilly LN, Fox AJ, Symons SP. Comparison of CTA to DSA in determining the etiology of spontaneous ICH. Can J Neurol Sci. 2009;36(2):176-80.
38. Thaker NG, Turner JD, Cobb WS, Hussain I, Janjua N, He W, et al. Computed tomographic angiography versus digital subtraction angiography for the postoperative detection of residual aneurysms: a single-institution series and meta-analysis. J Neurointerv Surg. 2012;4(3):219-25.
39. Heiserman JE, Dean BL, Hodak JA, Flom RA, Bird CR, Drayer BP, et al. Neurologic complications of cerebral angiography. AJNR Am J Neuroradiol. 1994;15(8):1401-7; discussion 8-11.
40. Cloft HJ, Joseph GJ, Dion JE. Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: a meta-analysis. Stroke. 1999;30(2):317-20.
41. Saboori M, Hekmatnia A, Ghazavi A, Basiratnia R, Omidifar N, Hekmatnia F, et al. The comparative study on diagnostic validity of cerebral aneurysm by computed tomography angiography versus digital subtraction angiography after subarachnoid hemorrhage. J Res Med Sci. 2011;16(8):1020-5.
42. Anderson GB, Steinke DE, Petruk KC, Ashforth R, Findlay JM. Computed tomographic angiography versus digital subtraction angiography for the diagnosis and early treatment of ruptured intracranial aneurysms. Neurosurgery. 1999;45(6):1315-20; discussion 20-2.
43. Howard BM, Hu R, Barrow JW, Barrow DL. Comprehensive review of imaging of intracranial aneurysms and angiographically negative subarachnoid hemorrhage. Neurosurg Focus. 2019;47(6):E20.
44. Mitchell P, Wilkinson ID, Hoggard N, Paley MN, Jellinek DA, Powell T, et al. Detection of subarachnoid haemorrhage with magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2001;70(2):205-11.
45. Ogawa T, Inugami A, Fujita H, Hatazawa J, Shimosegawa E, Noguchi K, et al. MR diagnosis of subacute and chronic subarachnoid hemorrhage: comparison with CT. AJR Am J Roentgenol. 1995;165(5):1257-62.
46. Rigamonti A, Ackery A, Baker AJ. Transcranial Doppler monitoring in subarachnoid hemorrhage: a critical tool in critical care. Can J Anaesth. 2008;55(2):112-23.
47. White H, Venkatesh B. Applications of transcranial Doppler in the ICU: a review. Intensive Care Med. 2006;32(7):981-94.
48. Rosen DS, Macdonald RL. Subarachnoid hemorrhage grading scales: a systematic review. Neurocrit Care. 2005;2(2):110-8.
49. Aulmann C, Steudl WI, Feldmann U. [Validation of the prognostic accuracy of neurosurgical admission scales after rupture of cerebral aneurysms]. Zentralbl Neurochir. 1998;59(3):171-80.
50. Oshiro EM, Walter KA, Piantadosi S, Witham TF, Tamargo RJ. A new subarachnoid hemorrhage grading system based on the Glasgow Coma Scale: a comparison with the Hunt and Hess and World Federation of Neurological Surgeons Scales in a clinical series. Neurosurgery. 1997;41(1):140-7; discussion 7-8.
51. Hunt WE, Kosnik EJ. Timing and perioperative care in intracranial aneurysm surgery. Clin Neurosurg. 1974;21:79-89.

52. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81-4.
53. Fischer J, Mathieson C. The history of the Glasgow Coma Scale: implications for practice. Crit Care Nurs Q. 2001;23(4):52-8.
54. Alvarez M, Nava JM, Rue M, Quintana S. Mortality prediction in head trauma patients: performance of Glasgow Coma Score and general severity systems. Crit Care Med. 1998;26(1):142-8.
55. Gotoh O, Tamura A, Yasui N, Suzuki A, Hadeishi H, Sano K. Glasgow Coma Scale in the prediction of outcome after early aneurysm surgery. Neurosurgery. 1996;39(1):19-24; discussion -5.
56. Ducati A. [The clinical grading of subarachnoid hemorrhage]. Minerva Anestesiol. 1998;64(4):109-12.
57. Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. J Neurosurg. 1988;68(6):985-6.
58. Rosen DS, Macdonald RL. Grading of subarachnoid hemorrhage: modification of the world World Federation of Neurosurgical Societies scale on the basis of data for a large series of patients. Neurosurgery. 2004;54(3):566-75; discussion 75-6.
59. Sano H, Inamasu J, Kato Y, Satoh A, Murayama Y, Diseases WC, et al. Modified world federation of neurosurgical societies subarachnoid hemorrhage grading system. Surg Neurol Int. 2016;7(Suppl 18):S502-3.
60. Smith ML, Abrahams JM, Chandela S, Smith MJ, Hurst RW, Le Roux PD. Subarachnoid hemorrhage on computed tomography scanning and the development of cerebral vasospasm: the Fisher grade revisited. Surg Neurol. 2005;63(3):229-34; discussion 34-5.
61. Reilly C, Amidei C, Tolentino J, Jahromi BS, Macdonald RL. Clot volume and clearance rate as independent predictors of vasospasm after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2004;101(2):255-61.
62. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, Jr., et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21-7; discussion -7.
63. Sherlock M, O'Sullivan E, Agha A, Behan LA, Rawluk D, Brennan P, et al. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. Clin Endocrinol (Oxf). 2006;64(3):250-4.
64. Chandy D, Sy R, Aronow WS, Lee WN, Maguire G, Murali R. Hyponatremia and cerebrovascular spasm in aneurysmal subarachnoid hemorrhage. Neurol India. 2006;54(3):273-5.
65. Qureshi AI, Suri MF, Sung GY, Straw RN, Yahia AM, Saad M, et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery. 2002;50(4):749-55; discussion 55-6.
66. Rahman M, Friedman WA. Hyponatremia in neurosurgical patients: clinical guidelines development. Neurosurgery. 2009;65(5):925-35; discussion 35-6.
67. Marr N, Yu J, Kutsogiannis DJ, Mahmoud SH. Risk of Hyponatremia in Patients with Aneurysmal Subarachnoid Hemorrhage Treated with Exogenous Vasopressin Infusion. Neurocrit Care. 2017;26(2):182-90.
68. Marupudi NI, Mittal S. Diagnosis and Management of Hyponatremia in Patients with Aneurysmal Subarachnoid Hemorrhage. J Clin Med. 2015;4(4):756-67.

69. Sayama T, Inamura T, Matsushima T, Inoha S, Inoue T, Fukui M. High incidence of hyponatremia in patients with ruptured anterior communicating artery aneurysms. Neurol Res. 2000;22(2):151-5.
70. Mount DB. The brain in hyponatremia: both culprit and victim. Semin Nephrol. 2009;29(3):196-215.
71. Hasan D, Wijdicks EF, Vermeulen M. Hyponatremia is associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. Ann Neurol. 1990;27(1):106-8.
72. Kruyt ND, Biessels GJ, de Haan RJ, Vermeulen M, Rinkel GJ, Coert B, et al. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage: a meta-analysis. Stroke. 2009;40(6):e424-30.
73. Kruyt ND, Biessels GJ, DeVries JH, Luitse MJ, Vermeulen M, Rinkel GJ, et al. Hyperglycemia in aneurysmal subarachnoid hemorrhage: a potentially modifiable risk factor for poor outcome. J Cereb Blood Flow Metab. 2010;30(9):1577-87.
74. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2012;43(6):1711-37.
75. Dorhout Mees SM, van Dijk GW, Algra A, Kempink DR, Rinkel GJ. Glucose levels and outcome after subarachnoid hemorrhage. Neurology. 2003;61(8):1132-3.
76. McGirt MJ, Woodworth GF, Ali M, Than KD, Tamargo RJ, Clatterbuck RE. Persistent perioperative hyperglycemia as an independent predictor of poor outcome after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2007;107(6):1080-5.
77. Douds GL, Tadzong B, Agarwal AD, Krishnamurthy S, Lehman EB, Cockroft KM. Influence of Fever and hospital-acquired infection on the incidence of delayed neurological deficit and poor outcome after aneurysmal subarachnoid hemorrhage. Neurol Res Int. 2012;2012:479865.
78. Albrecht RF, 2nd, Wass CT, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. Mayo Clin Proc. 1998;73(7):629-35.
79. Suehiro E, Sadahiro H, Goto H, Oku T, Oka F, Fujiyama Y, et al. Importance of Early Postoperative Body Temperature Management for Treatment of Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis. 2016;25(6):1482-8.
80. Reith J, Jorgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet. 1996;347(8999):422-5.
81. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, Ogilvy CS, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. Neurology. 2001;56(10):1299-304.
82. Dhar R, Diringer MN. The burden of the systemic inflammatory response predicts vasospasm and outcome after subarachnoid hemorrhage. Neurocrit Care. 2008;8(3):404-12.
83. Jane JA, Winn HR, Richardson AE. The natural history of intracranial aneurysms: rebleeding rates during the acute and long term period and implication for surgical management. Clin Neurosurg. 1977;24:176-84.
84. Starke RM, Connolly ES, Jr. Rebleeding after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;15(2):241-6.
85. Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. Stroke. 1994;25(7):1342-7.

86. Ameen AA, Illingworth R. Anti-fibrinolytic treatment in the pre-operative management of subarachnoid haemorrhage caused by ruptured intracranial aneurysm. J Neurol Neurosurg Psychiatry. 1981;44(3):220-6.
87. Tang C, Zhang TS, Zhou LF. Risk factors for rebleeding of aneurysmal subarachnoid hemorrhage: a meta-analysis. PLoS One. 2014;9(6):e99536.
88. Hasan D, Vermeulen M, Wijdicks EF, Hijdra A, van Gijn J. Management problems in acute hydrocephalus after subarachnoid hemorrhage. Stroke. 1989;20(6):747-53.
89. Hasan D, Lindsay KW, Vermeulen M. Treatment of acute hydrocephalus after subarachnoid hemorrhage with serial lumbar puncture. Stroke. 1991;22(2):190-4.
90. McIver JI, Friedman JA, Wijdicks EF, Piepgras DG, Pichelmann MA, Toussaint LG, 3rd, et al. Preoperative ventriculostomy and rebleeding after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002;97(5):1042-4.
91. Hellingman CA, van den Bergh WM, Beijer IS, van Dijk GW, Algra A, van Gijn J, et al. Risk of rebleeding after treatment of acute hydrocephalus in patients with aneurysmal subarachnoid hemorrhage. Stroke. 2007;38(1):96-9.
92. Kassell NF, Torner JC, Haley EC, Jr., Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg. 1990;73(1):18-36.
93. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S, et al. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. Neurol Res. 2009;31(2):151-8.
94. Lee KH, Lukovits T, Friedman JA. "Triple-H" therapy for cerebral vasospasm following subarachnoid hemorrhage. Neurocrit Care. 2006;4(1):68-76.
95. Wilkins RH. Cerebral vasospasm. Crit Rev Neurobiol. 1990;6(1):51-77.
96. Vora YY, Suarez-Almazor M, Steinke DE, Martin ML, Findlay JM. Role of transcranial Doppler monitoring in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery. 1999;44(6):1237-47; discussion 47-8.
97. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands. J Neurol Neurosurg Psychiatry. 2000;68(3):337-41.
98. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, et al. Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? Stroke. 2009;40(6):1963-8.
99. Kitazawa T, Eto M, Woodsome TP, Khalequzzaman M. Phosphorylation of the myosin phosphatase targeting subunit and CPI-17 during Ca2+ sensitization in rabbit smooth muscle. J Physiol. 2003;546(Pt 3):879-89.
100. Laher I, Zhang JH. Protein kinase C and cerebral vasospasm. J Cereb Blood Flow Metab. 2001;21(8):887-906.
101. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 1980;6(1):1-9.
102. Geraghty JR, Testai FD. Delayed Cerebral Ischemia after Subarachnoid Hemorrhage: Beyond Vasospasm and Towards a Multifactorial Pathophysiology. Curr Atheroscler Rep. 2017;19(12):50.
103. Rowland MJ, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. Br J Anaesth. 2012;109(3):315-29.

104. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke. 2010;41(10):2391-5.
105. Dankbaar JW, Rijsdijk M, van der Schaaf IC, Velthuis BK, Wermer MJ, Rinkel GJ. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neuroradiology. 2009;51(12):813-9.
106. Pham M, Johnson A, Bartsch AJ, Lindner C, Mullges W, Roosen K, et al. CT perfusion predicts secondary cerebral infarction after aneurysmal subarachnoid hemorrhage. Neurology. 2007;69(8):762-5.
107. Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S, et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. Stroke. 2008;39(11):3015-21.
108. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol. 2011;10(7):618-25.
109. Hart MN. Morphometry of brain parenchymal vessels following subarachnoid hemorrhage. Stroke. 1980;11(6):653-5.
110. Herz DA, Baez S, Shulman K. Pial microcirculation in subarachnoid hemorrhage. Stroke. 1975;6(4):417-24.
111. Koide M, Bonev AD, Nelson MT, Wellman GC. Subarachnoid blood converts neurally evoked vasodilation to vasoconstriction in rat brain cortex. Acta Neurochir Suppl. 2013;115:167-71.
112. Koide M, Bonev AD, Nelson MT, Wellman GC. Inversion of neurovascular coupling by subarachnoid blood depends on large-conductance Ca2+-activated K+ (BK) channels. Proc Natl Acad Sci U S A. 2012;109(21):E1387-95.
113. Wellman GC, Koide M. Impact of subarachnoid hemorrhage on parenchymal arteriolar function. Acta Neurochir Suppl. 2013;115:173-7.
114. Sehba FA, Friedrich V. Cerebral microvasculature is an early target of subarachnoid hemorrhage. Acta Neurochir Suppl. 2013;115:199-205.
115. Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A. Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. Neurochem Res. 1997;22(10):1249-55.
116. Frijns CJ, Fijnheer R, Algra A, van Mourik JA, van Gijn J, Rinkel GJ. Early circulating levels of endothelial cell activation markers in aneurysmal subarachnoid haemorrhage: associations with cerebral ischaemic events and outcome. J Neurol Neurosurg Psychiatry. 2006;77(1):77-83.
117. Budohoski KP, Guilfoyle M, Helmy A, Huuskonen T, Czosnyka M, Kirollos R, et al. The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2014;85(12):1343-53.
118. Vergouwen MD, Vermeulen M, Coert BA, Stroes ES, Roos YB. Microthrombosis after aneurysmal subarachnoid hemorrhage: an additional explanation for delayed cerebral ischemia. J Cereb Blood Flow Metab. 2008;28(11):1761-70.

119. Romano JG, Forteza AM, Concha M, Koch S, Heros RC, Morcos JJ, et al. Detection of microemboli by transcranial Doppler ultrasonography in aneurysmal subarachnoid hemorrhage. Neurosurgery. 2002;50(5):1026-30; discussion 30-1.
120. Giller CA, Giller AM, Landreneau F. Detection of emboli after surgery for intracerebral aneurysms. Neurosurgery. 1998;42(3):490-3; discussion 3-4.
121. Ikeda K, Asakura H, Futami K, Yamashita J. Coagulative and fibrinolytic activation in cerebrospinal fluid and plasma after subarachnoid hemorrhage. Neurosurgery. 1997;41(2):344-9; discussion 9-50.
122. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schutt S, et al. Inflammatory cytokines in subarachnoid haemorrhage: association with abnormal blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry. 2001;70(4):534-7.
123. Naredi S, Lambert G, Friberg P, Zall S, Eden E, Rydenhag B, et al. Sympathetic activation and inflammatory response in patients with subarachnoid haemorrhage. Intensive Care Med. 2006;32(12):1955-61.
124. Lee SJ, Benveniste EN. Adhesion molecule expression and regulation on cells of the central nervous system. J Neuroimmunol. 1999;98(2):77-88.
125. Sozen T, Tsuchiyama R, Hasegawa Y, Suzuki H, Jadhav V, Nishizawa S, et al. Role of interleukin-1beta in early brain injury after subarachnoid hemorrhage in mice. Stroke. 2009;40(7):2519-25.
126. Yamashita T, Abe K. Therapeutic approaches to vascular protection in ischemic stroke. Acta Med Okayama. 2011;65(4):219-23.
127. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. World Neurosurg. 2010;73(1):22-41.
128. Kubota T, Handa Y, Tsuchida A, Kaneko M, Kobayashi H, Kubota T. The kinetics of lymphocyte subsets and macrophages in subarachnoid space after subarachnoid hemorrhage in rats. Stroke. 1993;24(12):1993-2000; discussion -1.
129. Provencio JJ, Fu X, Siu A, Rasmussen PA, Hazen SL, Ransohoff RM. CSF neutrophils are implicated in the development of vasospasm in subarachnoid hemorrhage. Neurocrit Care. 2010;12(2):244-51.
130. Magnoni S, Stocchetti N, Colombo G, Carlin A, Colombo A, Lipton JM, et al. Alpha-melanocyte-stimulating hormone is decreased in plasma of patients with acute brain injury. J Neurotrauma. 2003;20(3):251-60.
131. Mathiesen T, Edner G, Ulfarsson E, Andersson B. Cerebrospinal fluid interleukin-1 receptor antagonist and tumor necrosis factor-alpha following subarachnoid hemorrhage. J Neurosurg. 1997;87(2):215-20.
132. Nakahara T, Tsuruta R, Kaneko T, Yamashita S, Fujita M, Kasaoka S, et al. High-Mobility Group Box 1 Protein in CSF of Patients with Subarachnoid Hemorrhage. Neurocritical Care. 2009;11(3):362.
133. Simard JM, Geng Z, Woo SK, Ivanova S, Tosun C, Melnichenko L, et al. Glibenclamide reduces inflammation, vasogenic edema, and caspase-3 activation after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2009;29(2):317-30.
134. Prunell GF, Svendgaard NA, Alkass K, Mathiesen T. Inflammation in the brain after experimental subarachnoid hemorrhage. Neurosurgery. 2005;56(5):1082-92; discussion -92.

135. Chou SH, Feske SK, Atherton J, Konigsberg RG, De Jager PL, Du R, et al. Early elevation of serum tumor necrosis factor-alpha is associated with poor outcome in subarachnoid hemorrhage. J Investig Med. 2012;60(7):1054-8.
136. Mathiesen T, Andersson B, Loftenius A, von Holst H. Increased interleukin-6 levels in cerebrospinal fluid following subarachnoid hemorrhage. J Neurosurg. 1993;78(4):562-7.
137. Fassbender K, Ries S, Schminke U, Schneider S, Hennerici M. Inflammatory cytokines in CSF in bacterial meningitis: association with altered blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry. 1996;61(1):57-61.
138. Ortega-Gutierrez S, Thomas J, Reccius A, Agarwal S, Lantigua H, Li M, et al. Effectiveness and safety of nicardipine and labetalol infusion for blood pressure management in patients with intracerebral and subarachnoid hemorrhage. Neurocrit Care. 2013;18(1):13-9.
139. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet. 2002;360(9342):1267-74.
140. Spetzler RF, McDougall CG, Albuquerque FC, Zabramski JM, Hills NK, Partovi S, et al. The Barrow Ruptured Aneurysm Trial: 3-year results. J Neurosurg. 2013;119(1):146-57.
141. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366(9488):809-17.
142. Boogaarts HD, van Amerongen MJ, de Vries J, Westert GP, Verbeek AL, Grotenhuis JA, et al. Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Neurosurg. 2014;120(3):605-11.
143. Pare L, Delfino R, Leblanc R. The relationship of ventricular drainage to aneurysmal rebleeding. J Neurosurg. 1992;76(3):422-7.
144. Gruber A, Reinprecht A, Bavinzski G, Czech T, Richling B. Chronic shunt-dependent hydrocephalus after early surgical and early endovascular treatment of ruptured intracranial aneurysms. Neurosurgery. 1999;44(3):503-9; discussion 9-12.
145. Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP. Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. Neurosurgery. 1982;11(3):337-43.
146. Awad IA, Carter LP, Spetzler RF, Medina M, Williams FC, Jr. Clinical vasospasm after subarachnoid hemorrhage: response to hypervolemic hemodilution and arterial hypertension. Stroke. 1987;18(2):365-72.
147. Friedman JA, Pichelmann MA, Piepgras DG, McIver JI, Toussaint LG, 3rd, McClelland RL, et al. Pulmonary complications of aneurysmal subarachnoid hemorrhage. Neurosurgery. 2003;52(5):1025-31; discussion 31-2.
148. Lopez-Arrieta JM, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. Cochrane Database Syst Rev. 2002(3):Cd000147.
149. Wessell A, Kole MJ, Badjatia N, Parikh G, Albrecht JS, Schreibman DL, et al. High Compliance with Scheduled Nimodipine Is Associated with Better Outcome in Aneurysmal Subarachnoid Hemorrhage Patients Cotreated with Heparin Infusion. Front Neurol. 2017;8:268.

150. Tomassoni D, Lanari A, Silvestrelli G, Traini E, Amenta F. Nimodipine and its use in cerebrovascular disease: evidence from recent preclinical and controlled clinical studies. Clin Exp Hypertens. 2008;30(8):744-66.
151. Scriabine A, van den Kerckhoff W. Pharmacology of nimodipine. A review. Ann N Y Acad Sci. 1988;522:698-706.
152. Auer LM, Oberbauer RW, Schalk HV. Human pial vascular reactions to intravenous Nimodipine-infusion during EC-IC bypass surgery. Stroke. 1983;14(2):210-3.
153. Keyrouz SG, Diringer MN. Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage. Crit Care. 2007;11(4):220.
154. Liu Y-f, Qiu H-C, Su J, Jiang W-J. Drug treatment of cerebral vasospasm after subarachnoid hemorrhage following aneurysms. Chinese Neurosurgical Journal. 2016;2(1):4.
155. Varsos VG, Liszczak TM, Han DH, Kistler JP, Vielma J, Black PM, et al. Delayed cerebral vasospasm is not reversible by aminophylline, nifedipine, or papaverine in a "two-hemorrhage" canine model. J Neurosurg. 1983;58(1):11-7.
156. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg. 1988;68(4):505-17.
157. Philippon J, Grob R, Dagreou F, Guggiari M, Rivierez M, Viars P. Acta Neurochir (Wien) (1986) 82:110-114 eCt ahirurgica Prevention of Vasospasm in Subarachnoid Haemorrhage. A Controlled Study with Nimodipine. 1986:110-4.
158. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989;298(6674):636-42.
159. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, et al. Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308(11):619-24.
160. Allen GS, Bahr AL. Cerebral arterial spasm: part 10. Reversal of acute and chronic spasm in dogs with orally administered nifedipine. Neurosurgery. 1979;4(1):43-7.
161. Allen GS, Banghart SB. Cerebral arterial spasm: part 9. In vitro effects of nifedipine on serotonin-, phenylephrine-, and potassium-induced contractions of canine basilar and femoral arteries. Neurosurgery. 1979;4(1):37-42.
162. Scr A, Bat R, Kazda S, Towart R, Schluter T, Ramsch K-d, et al. Nimodipine. 1985;3(28).
163. Solubility enhancement of nimodipine through preparation of Soluplus® dispersions. Journal of Applied Pharmaceutical Science. 2019;9(9):30-7.
164. Ms L, Em S. Nimodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs. 1989;37(5):669-99.
165. Towart R, Wehinger E, Meyer H, Kazda S. The effects of nimodipine, its optical isomers and metabolites on isolated vascular smooth muscle. Arzneimittelforschung. 1982;32(4):338-46.
166. <BSC CLASSIFICATION.pdf>.
167. Uchida S, Yamada S, Nagai K, Deguchi Y, Kimura R. Brain pharmacokinetics and in vivo receptor binding of 1,4-dihydropyridine calcium channel antagonists. Life Sci. 1997;61(21):2083-90.
168. Kazda S, Garthoff B, Krause HP, Schlossmann K. Cerebrovascular effects of the calcium antagonistic dihydropyridine derivative nimodipine in animal experiments. Arzneimittelforschung. 1982;32(4):331-8.

169. R.Towart EW, H.Meyer, and S.Kazda. The Effect of Nimodipine, its Optical Isomers and Metabolites on Isolated Vascular Smooth Muscle. ArzneimForsch/Drug Res. 1982;32(1):338-46.
170. Li RW, Tse CM, Man RY, Vanhoutte PM, Leung GP. Inhibition of human equilibrative nucleoside transporters by dihydropyridine-type calcium channel antagonists. Eur J Pharmacol. 2007;568(1-3):75-82.
171. Blardi P, Urso R, De Lalla A, Volpi L, Perri TD, Auteri A. Nimodipine: drug pharmacokinetics and plasma adenosine levels in patients affected by cerebral ischemia. Clin Pharmacol Ther. 2002;72(5):556-61.
172. Rudolphi KA, Schubert P, Parkinson FE, Fredholm BB. Neuroprotective role of adenosine in cerebral ischaemia. Trends Pharmacol Sci. 1992;13(12):439-45.
173. Sweeney MI. Neuroprotective effects of adenosine in cerebral ischemia: window of opportunity. Neurosci Biobehav Rev. 1997;21(2):207-17.
174. Langley MS, Sorkin EM. Nimodipine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs. 1989;37(5):669-99.
175. Muck W, Ahr G, Kuhlmann J. Nimodipine. Potential for drug-drug interactions in the elderly. Drugs & aging. 1995;6(3):229-42.
176. Ltd BA. PRODUCT INFORMATION NIMOTOP®. 2017.
177. Donald K. Woodward PD, Jimmi Hatton, Pharm.D., FCCP,, Mary H. H. Ensom PD, FCCP, Byron Young, M.D., Robert Dempsey, M.D., and, G. Dennis Clifton PD, FCCP. al-Acid Glycoprotein Concentrations and Cerebrospinal Fluid Drug Distribution after Subarachnoid Hemorrhage. Pharmacotherapy 1998;18(5):1062-68.
178. Adam P, Sobek O, Táborský L, Hildebrand T, Tutterová O, Zácek P. CSF and serum orosomucoid (alpha-1-acid glycoprotein) in patients with multiple sclerosis: a comparison among particular subgroups of MS patients. Clin Chim Acta. 2003;334(1-2):107-10.
179. Ha HR, Pletscher W, Leuenberger PM, Sticher O, Meier PJ. Measurement of Nimodipine Metabolism in Rat Liver Microsomes by High-Performance Liquid Chromatography. Journal of Liquid Chromatography. 2007;18(11):2243-55.
180. Scherling D, Bühner K, Krause HP, Karl W, Wünsche C. Biotransformation of nimodipine in rat, dog, and monkey. Arzneimittel-Forschung. 1991;41(4):392-8.
181. Rämsch KD, Ahr G, Tettenborn D, Auer LM. Overview on pharmacokinetics of nimodipine in healthy volunteers and in patients with subarachnoid hemorrhage. Neurochirurgia. 1985;28 Suppl 1:74-8.
182. Anonymous. Population pharmacokinetic analysis for nimodipine. Japanese Journal of Clinical Pharmacology and Therapeutics. 1999;30(1):229-30.
183. Becker C, Hilgert D, Platt D, Krauss D, Spahn H, Mutschler E. Pharmacokinetics of nimodipine and its major metabolites in elderly patients with cerebral disorders. European Journal of Pharmacology. 1990;183(6):2298.
184. Fischer C, Schonberger F, Muck W, Heuck K, Eichelbaum M. Simultaneous assessment of the intravenous and oral disposition of the enantiomers of racemic nimodipine by chiral stationary-phase high-performance liquid chromatography and gas chromatography/mass spectroscopy combined with a stable isotope technique. J Pharm Sci. 1993;82(3):244-50.
185. Michelson G, Wärntges S, Leidig S, Lötsch J, Geisslinger G. Nimodipine plasma concentration and retinal blood flow in healthy subjects. Investigative Ophthalmology & Visual Science. 2006;47(8):3479-86.

186. Muck W, Heine PR, Breuel HP, Niklaus H, Horkulak J, Ahr G. The effect of multiple oral dosing of nimodipine on glibenclamide pharmacodynamics and pharmacokinetics in elderly patients with type-2 diabetes mellitus. International Journal of Clinical Pharmacology and Therapeutics. 1995;33(2):89-94.
187. Wanner-Olsen H, Gaarskaer FB, Mikkelsen EO, Jakobsen P, Voldby B. Studies on concentration-time profiles of nimodipine enantiomers following intravenous and oral administration of nimodipine in patients with subarachnoid hemorrhage. Chirality. 2000;12(9):660-4.
188. Zisaki A, Miskovic L, Hatzimanikatis V. Antihypertensive drugs metabolism: an update to pharmacokinetic profiles and computational approaches. Curr Pharm Des. 2015;21(6):806-22.
189. Rämsch KD, Graefe KH, Scherling D, Sommer J, Ziegler R. Pharmacokinetics and metabolism of calcium-blocking agents nifedipine, nitrendipine, and nimodipine. Am J Nephrol. 1986;6 Suppl 1:73-80.
190. Abboud T, Andresen H, Koeppen J, Czorlich P, Duehrsen L, Stenzig J, et al. Serum levels of nimodipine in enteral and parenteral administration in patients with aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien). 2015;157(5):763-7.
191. Carcas AJ, Abad-Santos F, De Rosendo JM, Frias J. Nimodipine transfer into human breast milk and cerebrospinal fluid. Annals of Pharmacotherapy. 1996;30(2):148-50.
192. Hynynen M, Siltanen T, Sahlman A, Pohjasvaara T, Muck W, Kaste M. Continuous infusion of nimodipine during coronary artery surgery: Haemodynamic and pharmacokinetic study. British Journal of Anaesthesia. 1995;74(5):526-33.
193. Jakobsen P, Mikkelsen EO, Laursen J, Jensen F. Determination of nimodipine by gas chromatography using electron-capture detection; External factors influencing nimodipine concentrations during intravenous administration. Journal of Chromatography - Biomedical Applications. 1986;374(2):383-7.
194. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European Journal of Clinical Pharmacology. 1993;45(4):363-6.
195. Ramsch KD, Graefe KH, Scherling D. Pharmacokinetics and metabolism of calcium-blocking agents nifedipine, nitrendipine, and nimodipine. American Journal of Nephrology. 1986;6(SUPPL. 1):73-80.
196. Scheller C, Vogel AS, Simmermacher S, Rachinger JC, Prell J, Strauss C, et al. Prophylactic intravenous nimodipine treatment in skull base surgery: pharmacokinetic aspects. Journal Of Neurological Surgery Part A, Central European Neurosurgery. 2012;73(3):153-9.
197. Scheller C, Wienke A, Wurm F, Vogel AS, Simmermacher S, Prell J, et al. Enteral or parenteral nimodipine treatment: A comparative pharmacokinetic study. Journal of Neurological Surgery, Part A: Central European Neurosurgery. 2014;75(2):84-90.
198. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage – a pilot study. European Journal of Clinical Pharmacology. 2007;63:355-61.
199. Steudel WI, Carvi M, Lorenz R. Prognostic significance of the concentration of nimodipine in the CSF and plasma in acute subarachnoid hemorrhage. New Trends in Clinical Neuropharmacology. 1989;3(2):100.
200. Vinge E, Andersson KE, Brandt L. Pharmacokinetics of nimodipine in patients with aneurysmal subarachnoid haemorrhage. European Journal of Clinical Pharmacology. 1986;30(4):421-5.

201. Sramek JJ, Heller AH, Sundaresan PR, Lettieri J, Sawin S, Cutler NR. Safety and tolerance of intravenous nimodipine. Ann Pharmacother. 1994;28(10):1143-8.
202. Fleishaker JC, Hulst LK, Peters GR. Lack of a pharmacokinetic/pharmacodynamic interaction between nimodipine and tirilazad mesylate in healthy volunteers. Journal Of Clinical Pharmacology. 1994;34(8):837-41.
203. Gengo FM, Fagan SC, Krol G, Bernhard H. Nimodipine disposition and haemodynamic effects in patients with cirrhosis and age-matched controls. British Journal of Clinical Pharmacology. 1987;23(1):47-53.
204. Gualano V, Ntsikoussalabongui B, Mignot A, Duvauchelle T, Felices M, Guillaume M, et al. Comparative bioavailability of two oral nimodipine formulations after administration to 24 healthy volunteers. Clinical Drug Investigation. 1999;17(6):475-82.
205. He Z, Zhong D, Chen X, Liu X, Tang X, Zhao L. Development of a dissolution medium for nimodipine tablets based on bioavailability evaluation. European Journal Of Pharmaceutical Sciences: Official Journal Of The European Federation For Pharmaceutical Sciences. 2004;21(4):487-91.
206. Liu XD, Xie L, Xu GQ, Wang J, Zhou YC, Liu GQ. Variability of nimodipine pharmacokinetics in healthy Chinese males. Chinese Journal of Pharmacology and Toxicology. 1996;10(1):25-7.
207. Muck W, Tanaka T, Ahr G, Kuhlmann J. No interethnic differences in stereoselective disposition of oral nimodipine between Caucasian and Japanese subjects. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(4):163-71.
208. Qin F, Ma Y, Wang Y, Chen L, Wang D, Li F. Determination of nimodipine in human plasma by ultra performance liquid chromatography-tandem mass spectrometry and pharmacokinetic application. Journal of Pharmaceutical and Biomedical Analysis. 2008;46(3):557-62.
209. Qiu F, Chen X, Li X, Zhong D. Determination of nimodipine in human plasma by a sensitive and selective liquid chromatography-tandem mass spectrometry method. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences. 2004;802(2):291-7.
210. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, et al. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. British Journal Of Clinical Pharmacology. 1991;32(3):335-40.
211. Zhao Y, Zhai D, Chen X, Yu Q, He H, Sun Y, et al. Determination of nimodipine in human plasma by HPLC-ESI-MS and its application to a bioequivalence study. Journal of Chromatographic Science. 2010;48(2):81-5.
212. 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. European Journal Of Clinical Pharmacology. 2009;65(6):579-84.
213. Breuel HP, Muck W, Heine PR, Schmage N, Niklaus H, Kuhlmann J. The influence of nimodipine on hemodynamic parameters and peak and trough plasma concentrations of nifedipine chronically administered to elderly hypertensive patients. International Journal of Clinical Pharmacology and Therapeutics. 1995;33(2):109-13.
214. Eicher H, Hilgert D, Zeeh J, Platt D, Becker C, Mutschler E. Pharmacokinetics of nimodipine in multimorbid elderly patients with chronic brain failure. Archives of Gerontology and Geriatrics. 1992;14(3):309-19.

215. Heine PR, Weyer G, Breuel HP, Muck W, Schmage N, Kuhlmann J. Lack of interaction between diazepam and nimodipine during chronic oral administration to healthy elderly subjects. British Journal of Clinical Pharmacology. 1994;38(1):39-43.
216. Hernández-Hernández R, Coll T, Rachitzky P, Armas-Hernández MJ, Armas-Padilla MC, Velasco M, et al. Comparison of two nimodipine formulations in healthy volunteers. Journal Of Human Hypertension. 2002;16 Suppl 1:S142-S4.
217. Kirch W, Ramsch KD, Duhrsen U, Ohnhaus EE. Clinical pharmacokinetics of nimodipine in normal and impaired renal function. International Journal of Clinical Pharmacology Research. 1984;4(5):381-4.
218. Muck W, Breuel HP, Kuhlmann J. The influence of age on the pharmacokinetics of nimodipine. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(7):293-8.
219. Muck W, Heine PR, Schmage N, Niklaus H, Horkulak J, Breuel HP. Steady-state pharmacokinetics of nimodipine during chronic administration of indometacin in elderly healthy volunteers. Arzneimittel-Forschung/Drug Research. 1995;45(4):460-2.
220. Mück W, Wingender W, Seiberling M, Woelke E, Rämsch KD, Kuhlmann J. Influence of the H2-receptor antagonists cimetidine and ranitidine on the pharmacokinetics of nimodipine in healthy volunteers. European Journal Of Clinical Pharmacology. 1992;42(3):325-8.
221. Terziivanov D, Atanasova I, Dimitrova V, Robeva R, Unger S, Muck W. Pharmacokinetic variability of nimodipine disposition after single and multiple oral dosing to hypertensive renal failure patients: Parametric and nonparametric population analysis. International Journal of Clinical Pharmacology and Therapeutics. 1999;37(8):404-12.
222. W.Muck HPB, J.Kuhlmann. The influence of age on pharmacokinetics of nimodipine*. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(7):293-8.
223. Eicher H, Hilgert D, Zeeh J, Platt D, Becker C, Mutschler E. Pharmacokinetics of nimodipine in multimorbid elderly patients with chronic brain failure. Arch Gerontol Geriatr. 1992;14(3):309-19.
224. Vinge E, Andersson KE, Brandt L, Ljunggren B, Nilsson LG, Rosendal-Helgesen S. Pharmacokinetics of nimodipine in patients with aneurysmal subarachnoid haemorrhage. European Journal Of Clinical Pharmacology. 1986;30(4):421-5.
225. Albanna W, Weiss M, Conzen C, Clusmann H, Schneider T, Reinsch M, et al. Systemic and Cerebral Concentration of Nimodipine During Established and Experimental Vasospasm Treatment. World Neurosurg. 2017.
226. Kirch W, Rämsch KD, Dührsen U, Ohnhaus EE. Clinical pharmacokinetics of nimodipine in normal and impaired renal function. International Journal Of Clinical Pharmacology Research. 1984;4(5):381-4.
227. Terziivanov D, Atanasova I, Dimitrova V, Robeva R, Unger S, Mück W. Pharmacokinetic variability of nimodipine disposition after single and multiple oral dosing to hypertensive renal failure patients: parametric and nonparametric population analysis. International Journal Of Clinical Pharmacology And Therapeutics. 1999;37(8):404-12.
228. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, et al. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. British Journal of Clinical Pharmacology. 1991;32(3):335-40.
229. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage - a pilot study. European Journal Of Clinical Pharmacology. 2007;63(4):355-61.

230. Fuhr U, Maier-Brüggemann A, Blume H, Mück W, Unger S, Kuhlmann J, et al. Grapefruit juice increases oral nimodipine bioavailability. International Journal Of Clinical Pharmacology And Therapeutics. 1998;36(3):126-32.
231. Heine PR, Weyer G, Breuel HP, Mück W, Schmage N, Kuhlmann J. Lack of interaction between diazepam and nimodipine during chronic oral administration to healthy elderly subjects. British Journal Of Clinical Pharmacology. 1994;38(1):39-43.
232. Breuel HP, Heine PR, Mück W, Niklaus H, Schmage N, Kuhlmann J. Chronic administration of nimodipine and propranolol in elderly normotensive subjects--an interaction study. International Journal Of Clinical Pharmacology And Therapeutics. 1995;33(2):103-8.
233. Bruderer S, Zisowsky J, Fuseau E, Gutierez M, Dingemanse J. Investigation of pharmacokinetic and pharmacodynamic interactions between clazosentan and nimodipine in asah patients: A population analysis. Basic and Clinical Pharmacology and Toxicology. 2011;109:150.
234. Nimotop(monograph).Mississauga, Ontario: Bayer Inc; 2014.12.
235. Abboud T, Regelsberger J. Serum Levels of Nimodipine in Enteral and Parenteral Administration in Patients with Aneurysmal Subarachnoid Hemorrhage. Acta Neurochir (Wien). 2015;157(7):1133-4.
236. Schmith VD, Foss JF. Effects of inflammation on pharmacokinetics/pharmacodynamics: increasing recognition of its contribution to variability in response. Clin Pharmacol Ther. 2008;83(6):809-11.
237. 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):238-42.
238. Riva R, Pegoli M, Contin M, Perrone A, Mohamed S, Zanello M. Cerebrospinal Fluid Concentrations of Nimodipine Correlate With Long-term Outcome in Aneurysmal Subarachnoid Hemorrhage: Pilot Study. Clin Neuropharmacol. 2019.
239. Soppi V, Karamanakos PN, Koivisto T, Kurki MI, Vanninen R, Jaaskelainen JE, et al. A randomized outcome study of enteral versus intravenous nimodipine in 171 patients after acute aneurysmal subarachnoid hemorrhage. World Neurosurg. 2012;78(1-2):101-9.
240. Kronvall E, Undren P, Romner B, Saveland H, Cronqvist M, Nilsson OG. Nimodipine in aneurysmal subarachnoid hemorrhage: a randomized study of intravenous or peroral administration. J Neurosurg. 2009;110(1):58-63.
241. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. European journal of clinical pharmacology. 1993;45(4):363-6.
242. Kumana CR, Kou M, Yu YL, Fong KY, Fung CF, Chang CM, et al. Investigation of nimodipine pharmacokinetics in Chinese patients with acute subarachnoid haemorrhage. Eur J Clin Pharmacol. 1993;45(4):363-6.
243. Fischer C, Schönberger F, Mück W, Heuck K, Eichelbaum M. Simultaneous assessment of the intravenous and oral disposition of the enantiomers of racemic nimodipine by chiral stationary-phase high-performance liquid chromatography and gas chromatography/mass spectroscopy combined with a stable isotope technique. J Pharm Sci. 1993;82(3):244-50.
244. Wanner-Olsen H, Gaarskær FB, Mikkelsen EO, Jakobsen P, Voldby B. Studies on concentration-time profiles of nimodipine enantiomers following intravenous and oral administration of nimodipine in patients with subarachnoid hemorrhage. Chirality. 2000;12(9):660-4.

245. Muck WM. Enantiospecific determination of nimodipine in human plasma by liquid chromatography-tandem mass spectrometry. Journal of Chromatography A. 1995;712(1):45-53.
246. Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. Crit Care. 2016;20(1):277.
247. NIMOTOP(R) Product Monograph, Mississauga, Ontario. Bayer Inc.; 2014.
248. Abboud T, Andresen H, Koeppen J, Czorlich P, Duehrsen L, Stenzig J, et al. Serum levels of nimodipine in enteral and parenteral administration in patients with aneurysmal subarachnoid hemorrhage. Acta Neurochirurgica. 2015;157(5):763-7.
249. Bardelmeijer HA, van Tellingen O, Schellens JH, Beijnen JH. The oral route for the administration of cytotoxic drugs: strategies to increase the efficiency and consistency of drug delivery. Invest New Drugs. 2000;18(3):231-41.
250. Beierle I, Meibohm B, Derendorf H. Gender differences in pharmacokinetics and pharmacodynamics. Int J Clin Pharmacol Ther. 1999;37(11):529-47.
251. Katsura T, Inui K. Intestinal absorption of drugs mediated by drug transporters: mechanisms and regulation. Drug Metab Pharmacokinet. 2003;18(1):1-15.
252. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
253. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin. 2006;22(2):255-71, vi.
254. Jamali F, Kunz-Dober CM. Pain-mediated altered absorption and metabolism of ibuprofen: an explanation for decreased serum enantiomer concentration after dental surgery. Br J Clin Pharmacol. 1999;47(4):391-6.
255. Dorhout Mees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007(3):CD000277.
256. Krol GJ, Noe AJ, Yeh SC, Raemsch KD. Gas and liquid chromatographic analyses of nimodipine calcium antagonist in blood plasma and cerebrospinal fluid. J Chromatogr. 1984;305(1):105-18.
257. Mohamed S, Riva R, Contin M. Simple and validated UHPLC-MS/MS analysis of nimodipine in plasma and cerebrospinal fluid of patients with subarachnoid haemorrhage. J Chromatogr B Analyt Technol Biomed Life Sci. 2016;1028:94-9.
258. do Nascimento DF, de Moraes MO, Bezerra FAF, Pontes AV, Uchoa CRA, de Moraes RA, et al. Determination of nimodipine in plasma by HPLC-MS/MS and pharmacokinetic application. Brazilian Journal of Pharmaceutical Sciences. 2010;46(4):665-77.
259. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604-7.
260. Soppi V, Kokki H, Koivisto T, Lehtonen M, Helin-Tanninen M, Lehtola S, et al. Early-phase pharmacokinetics of enteral and parenteral nimodipine in patients with acute subarachnoid haemorrhage-a pilot study.
261. Isse FA, Abdallah YEH, Mahmoud SH. The Impact of Nimodipine Administration through Feeding Tube on Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage. J Pharm Pharm Sci. 2020;23(1):100-8.