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Research Article

Controversies on Dosing of Prophylactic Nimodipine in Subarachnoid Haemorrhage, a Narrative Review

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ABSTRACT

The use of nimodipine for the prophylaxis of neurological complications related to angiographic vasospasm has been a common practice for more than four decades. However, only few trials demonstrated an outcome benefit, defined as a reduction in mortality and vegetative states. By contemporary standards, these benefits may be considered marginal. The controversies regarding the use of nimodipine relate to its mechanism of action, the idiosyncratic factors involved in its effects and the current use of a standardised dose. Furthermore, the multifactorial nature of Delayed Cerebral Ischemia (DCI) adds ambiguity on its clinical endpoints. Consequently, the absence of a specific clinical target limits the capacity to describe a therapeutic plasma level of nimodipine, thus restricting the attainment of individualised dosing. This review aims to consolidate evidence regarding nimodipine dosing and its pharmacokinetic profile, identifying knowledge gaps to guide the design of future studies focused on optimising nimodipine dosing. We conducted a search using Medline, Embase, Cochrane, Web of Science, and PubMed search engines. We narrowed the search to experimental and clinical studies focusing on dose-regimens of nimodipine. A total of 16 experimental studies, 23 clinical studies, and 8 dose-response experimental and clinical trials were reviewed. Limitations related to route of administration, dose, bioavailability, drug clearance, and clinical endpoints were identified. We concluded that the considerable variability in nimodipine's pharmacokinetics may result in suboptimal dosing for SAH patients. Re-evaluation of the current standardised dosing regimen of nimodipine and the consideration of the potential benefits of personalised dosing are warranted.

Keywords: Nimodipine dose-response; Variability; Clearance; Optimal dosing

INTRODUCTION

Nimodipine, a lipophilic dihydropyridine calcium channel blocker, effectively crosses the Blood Brain Barrier (BBB), offering selective effects in cerebral regions. Its mechanism of action involves blocking the influx of extracellular calcium into the cytoplasm through L-type voltage-gated channels, minimising intracellular calcium overload in ischemic neurons. Nimodipine specifically targets the pial vessels, increasing collateralisation in ischemic conditions. Additionally, nimodipine modulates the predisposing influx of neuronal calcium, which has been associated with cell death, massive neuronal depolarization and activation of calcium channels leading to irreversible ischemic injury. Furthermore, nimodipine induces vasodilation at lower plasma concentrations than other dihydropyridines, a feature that has led to the conception of nimodipine having a "neuroprotective effect." However, clinical studies have postulated that its beneficial effects may involve additional pathways, that resolution of angiographic vasospasm does not correlate with clinical outcomes, and that Delayed Cerebral

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Ischemia (DCI) is multifactorial, questioning the key role of nimodipine on the overall treatment of Subarachnoid Haemorrhage (SAH).

Controversies regarding the mechanism of action of nimodipine are outweighed by those concerning its dosing, which has remained unchanged since the original Randomised Control Trials (RCTs) conducted four decades ago. These trials primarily demonstrated a reduction in death and vegetative states as their endpoints, outcomes that may now be considered unsatisfactory or insufficient for managing a prevalent condition such as SAH. Initially, a weight-adjusted dose was proposed; however, the trials eventually recommended a standard enteral dose for all patients, irrespective of variations in weight, renal function, or liver clearance. This standardised dosing approach may have led to over-dosing in some patients and under-dosing in others, potentially causing increased side effects or negligible therapeutic effects, respectively. Moreover, given the multifactorial aetiology of DCI, defining nimodipine's clinical target becomes challenging. Consequently, without a clear therapeutic goal, determining nimodipine's optimal plasma level and dose remains difficult [1].

This review aims to explore the potential benefits of individually adjusting nimodipine dosing through Therapeutic Drug Monitoring (TDM) to optimise its efficacy and minimise side effects. It will systematically compile evidence on nimodipine's pharmacokinetic profile and dosing regimens, with the aim of identifying knowledge gaps to inform the design of future studies focused on determining the optimal dosing for nimodipine [2].

MATERIALS AND METHODS

Search strategy

PubMed, EMBASE, Web of Science, and Cochrane, accessed through the library tools of the University of Queensland, were searched with no initial search restrictions. The search process included several stages: An initial Medline search identified relevant keywords; subsequent literature searches used these keywords. Reference lists from included articles and key author searches were then completed. Results from three database searches, using overlapping filters and criteria, were combined and duplicates were removed. The search included terms such as: "subarachnoid hemorrhage", "subarachnoid haemorrhage", "nimodipine" OR "calcium channel blockers", AND "dose response" OR "dose response relationship", including Medical Subject Headings (MeSH) terms. These search terms were implemented with Boolean operators "AND" (to combine "subarachnoid hemorrhage", "subarachnoid haemorrhage" with "nimodipine") and "OR" (when referring to "nimodipine" OR "calcium channel blockers", as well as "dose response" OR "dose response relationship"). We also conducted an extensive literature search, narrowing from the broad topic of "subarachnoid hemorrhage" to the specific "dose response of nimodipine", using additional filters and advanced search techniques. Our goal was to conduct the most specific and comprehensive data search possible to ensure inclusion of all relevant pharmacokinetic and dose-regimens studies. A previous scoping review on nimodipine was registered with the PROSPERO international prospective register (PROSPERO registration number CRD42020188319), serving as the source for all publications related to the prophylactic role and dosing regimens of nimodipine [3].

Selection criteria

Study records, data management and selection process: Two investigators (JP and JB) independently screened the selected abstracts to identify studies that focused on: Dosing of nimodipine in SAH; Pharmacokinetic and Pharmacodynamic (PK/PD) data; dose-response to nimodipine; pathway of administration (either enteral or parenteral); and nimodipine concentrations in plasma and/or in Cerebrospinal Fluid (CSF). Both experimental and clinical studies were included.

Types of studies: Studies published from January 1, 1980, to the current date and publications written in English were included. The following were excluded: Publications prior to the inclusion date; studies focusing solely on the radiological response to nimodipine, specifically those using intraarterial nimodipine for the treatment of established angiographic vasospasm; and studies based on the general management of SAH as opposed to the focused dose-effect of nimodipine [4].

Data extraction: Data were extracted in duplicate by two reviewers (JP and JB). When necessary, input from a senior librarian was sought to ensure maximum robustness of the search. The data extracted included the year and language of publication, the country where studies were conducted, the type of study, and patient enrolment. The focus of the extraction was on dose-regimens of nimodipine intended for prophylactic use.

Data synthesis: Studies were grouped by study type (experimental versus clinical studies); intervention; description of nimodipine's dose-regimen; pharmacokinetic parameters; dosing regimen; confirmation of angiographic vasospasm; and changes in hemodynamic parameters. The characteristics of the studies are presented in summary Tables 1-3.

Historical progress: Studies on nimodipine dosing

Experimental pre-clinical dosing studies: Prior to 1981, the use of nimodipine was primarily supported by expert communications and small studies conducted on healthy volunteers. However, significant advancements were made from that point onwards with the initiation of experimental pre-clinical dosing studies. Experimental models in SAH conducted on animals such as cats, primates, dogs, rats and rabbits demonstrated the selective effect of nimodipine on cerebral vasodilation. These studies revealed a substantial increase in Cerebral Blood Flow (CBF) and collateralisation in regions subjected to ischemia. Interestingly, these pioneering studies used a weight-adjusted dose of nimodipine, administered either intravenously or enterally. Researchers proposed that 4 µg/kg/min was the peak dose of nimodipine that maximised CBF without inducing systemic hypotension. Additionally, administering a dose of 0.5 to 1 µg/kg/min as an infusion in subjects with systemic hypertension led to an increase in CBF, suggesting a loss of cerebral autoregulation. Another study

highlighted the ability of nimodipine to selectively enhance CBF in regions with increased cerebral vascular resistance. Takayasu and colleagues determined that the mean concentration of nimodipine required to achieve 50% cerebral vasodilation, selectively at the pial regions, was 1.6 nmol/L. Other pioneering studies explored regional administration of nimodipine and investigated the time-course kinetics and location of specific receptors. This body of evidence from pre-clinical studies laid the foundation for subsequent clinical investigations. In 1989, Langley and colleagues published the first pharmacokinetic review, which established a dosing regimen for nimodipine for the first time. This regimen consists of a starting dose of 1 mg/h, followed by an infusion of 2 mg/h for 21 days. Alternatively, patients could receive 60 mg administered every 4 h, a regimen that has persisted to the current date [5].

Original clinical dosing studies: Clinical studies conducted by Auer, et al. introduced a series of pioneering investigations using 180-to-200 μg topical nimodipine and weight-adjusted doses of 1 μg/kg/min intravenous solutions amongst SAH patients. These studies revealed a selective vasodilatory effect on vessels of small diameter and those exposed during surgical clipping. Furthermore, these studies also highlighted that angiographic vasospasm does not necessarily correlate with neurological deficits. Both findings contributed to the design of future studies and provided insights into the pathophysiology of SAH. Additional research employing weight-adjusted regimens demonstrated a significant difference between nimodipine concentrations in plasma and the CSF compartment, laying the groundwork for recent large-scale clinical trials. Moreover, Genko and collaborators illustrated how nimodipine's variability can influence its clearance, particularly amongst patients with chronic liver disease, emphasising a crucial consideration for optimal and individualised dosing strategies.

An original pharmacokinetic study by Vinge, et al. amongst SAH patients receiving intravenous nimodipine infusion used a combined regimen of 7 days of infusion at 2 mg/h, followed by enteral administration of 45 mg every 6 h for an additional seven days. This study revealed a mean plasma concentration of 26.6 ± 1.8 ng/mL, with an observed inverse relation between plasma clearance and age. The study reported a peak nimodipine level occurring 1 h after initiation, though the peak varied considerably, ranging from 7.0 to 96.0 ng/mL, with a mean bioavailability of 15.9%. Except for two patients, all participants had normal renal and liver function. Remarkably, the plasma concentration of nimodipine did not differ between patients experiencing DCI-related complications and those without. Importantly, blood samples for nimodipine measurements were handled in a light-protected manner, a methodological consideration undisclosed in many studies. These methodological variations amongst studies, including differences in how nimodipine levels were measured, could potentially be a confounder in the interpretation of historical studies. Clinical studies based on administration pathways [6].

Clinical studies based on administration pathways

Enteral pharmacokinetics studies: Nimodipine is rapidly absorbed with peak concentrations reached within 0.5–1.5 h post-dose. However, due to significant first-pass metabolism, nimodipine exhibits reduced oral bioavailability, estimated at approximately 13%, which is further reduced in the presence of enteral intake. Few studies have highlighted the considerable variability in oral bioavailability, ranging from 3 to 30%, while emphasising a proportional relationship between its administered dose and Area under the Curve (AUC). These findings hold particular importance in the context of modified dosing regimens, such as those employing 30 mg every 2 h, aimed at mitigating the risk of systemic hypotension or amongst patients receiving crushed tablets through nasogastric feeding tubes.

Nimodipine is metabolised in the liver through CYP3A4 and CYP3A5 and has a short half-life of 1-2 h, requiring regular dosing intervals. Metabolic pathways involve demethylation and dehydrogenation of the dihydropyridine nucleus, producing inactive pyridine analogues that are further metabolised prior to excretion. Biotransformation of nimodipine produces more than 18 metabolites that undergo excretion and reabsorption, contributing to its variable plasma concentrations. Patients with liver dysfunction experience impaired clearance and increased exposure of nimodipine, requiring dose-adjustments, although clinical practice often overlooks this consideration. Nimodipine is predominantly excreted within 9 h after ingestion through bile and faeces, with less than 1% excreted unchanged through the kidneys. However, renal failure leads to reduced clearance and prolonged elimination half-life (22 h versus 8 h in healthy individuals), also, a factor frequently underestimated in clinical settings [7].

Parenteral pharmacokinetics studies: Following intravenous administration, the Volume of distribution (Vd) of nimodipine exhibits significant variability, estimated within a range of 0.94 to 2.46 L/kg. Furthermore, nimodipine demonstrates a high serum protein binding rate of 95%, particularly to ALPHA-ACID Glycoprotein (AAG). This high protein binding presents an important consideration and a potential limitation on the therapeutic efficacy of nimodipine, especially amongst critically ill patients in a catabolic state or with hypoproteinemia. However, to date, no studies have directly correlated the levels of AAG with plasma concentrations of nimodipine. As such, while the relation remains theoretical, its clinical implications remain unproven.

Despite the complete bioavailability of intravenous nimodipine, only a small proportion penetrates the CSF, resulting in a CSF-to-blood concentration gradient ranging from 0.3 to 77 μg/L. The compartmental distribution of nimodipine may contribute to its effects; however, studies focusing on achieving high nimodipine levels at the subarachnoid space have not demonstrated differences in neurological outcomes compared to standard administration regimens and dosages [8].

Furthermore, intravenous nimodipine maintains stable plasma concentrations. However, its use must be weighed against the higher cost and limited outcome data for intravenous regimens. Few RCTs comparing enteral and parenteral administration have indicated no significant differences in outcomes on an established dosing regimen of 1 mg/h infusion during the first 2 h, followed by a 2 mg/h infusion over the first 21 days. A recent

meta-analysis evaluating the efficacy of intravenous nimodipine has suggested that whilst the clinical benefit of nimodipine is established with enteral regimens, there is paucity of data supporting parenteral administration, indicating the need for further research to determine the exact role of intravenous nimodipine in current practice [9].

Intraventricular administration studies: RCTs such as the Newton-2 trial and the Carlson, et al. trial, have investigated the efficacy and safety of a single administration of 600 mg of EG-1962 microparticles (sustained release formulation of nimodipine) into the intraventricular space compared to standard oral nimodipine regimen in SAH patients. These trials primarily assessed neurological outcomes at 90 days as the main endpoint. However, they found that sustained release nimodipine, administered *via* an External Ventricular Drain (EVD), did not confer significant neurological benefits compared to standard of care. Previous experimental studies assessing the effect of locally administered slow-release nimodipine micro-particles transitioned into clinical trials focusing on outcome, dosage, and duration of intraventricular nimodipine administration. The original Newton-1 trial demonstrated that a single intraventricular injection of EG-1962 equivalent to 800 mg of nimodipine was the Maximal Dose Tolerated (MDT) without causing systemic hypotension or significant intracranial complications such as meningitis, ventriculitis, or increased Intracranial Pressure (ICP). While the intraventricular injection of EG-1962 was associated with reduced angiographic vasospasm, infarction, and the need for rescue therapies compared to standard oral therapy, it's important to note that the Newton-1 trial was a pilot feasibility study not focused on differences in outcomes. Most recent trials comparing the efficacy and safety of a single intra-cisternal administration of nimodipine microparticles to standard of care in SAH patients have similarly shown that sustained-release nimodipine administered *via* an external ventricular drain did not provide additional outcome benefits compared to standard regimens.

Pharmacokinetics on special populations

Nimodipine in elderly patients: Prospective pharmacokinetics studies conducted in patients across distinctive age-ranges have revealed no significant differences in pharmacokinetic parameters between groups when nimodipine was administered intravenously. However, elderly patients exhibited higher observed plasma concentration (C_{max}) and AUC values with oral nimodipine, suggesting that the first-pass metabolism of nimodipine is affected by age. Additionally, another study indicated that nimodipine clearance was reduced amongst elderly patients, potentially attributable to age-related declines in renal function.

Nimodipine in patients with liver disfunction: Patients with liver disfunction exhibit an increased AUC compared to healthy volunteers, attributed to impaired clearance. A study demonstrated that in patients with cirrhosis, the standard oral dose of nimodipine resulted in reduced clearance and significantly higher C_{max} values compared to patients with normal liver function. In this setting, dose-adjustments may be required for this population; however, current clinical practice does not involve monitoring plasma levels to optimise nimodipine dosing in patients with liver dysfunction.

Nimodipine in patients with renal failure: The urinary excretion of nimodipine primarily occurs as metabolites and is delayed in patients with renal failure. Two studies have demonstrated that in populations with chronic renal failure (defined by a glomerular filtration rate of less than 60 mL/min), the C_{max} of nimodipine is higher, and the half-life is prolonged. These findings contribute to the variable pharmacokinetic profile of nimodipine. However, current clinical practice does not involve monitoring plasma levels to optimise nimodipine dosing in patients with renal failure.

Dose-response studies

Pre-clinical studies with experimental models have challenged the hypothesis of an optimal dose-response for nimodipine. These studies have shown that the vasodilatory effect of nimodipine remains consistent whether administered intraluminal or extraluminally. Furthermore, it was found that the optimal topical dose of nimodipine for both spastic and non-spastic cerebral arterioles fall within the range of 1-100 nM when administered extraluminally, with higher doses yielding only marginal effects. These studies also demonstrated that sustained vasoconstriction of cerebral arterioles following SAH induces an endothelial remodelling, the long-term consequences of which are yet unknown. Additionally, under these conditions, there is downregulation of the voltage-dependant ion channels, which increases their resistance to L-type calcium channel blockers like nimodipine. This phenomenon limits the efficacy of nimodipine and could pose significant clinical concerns for patients who experience symptomatic responses to nimodipine and require vasopressor support, as well as those undergoing induced hypertension or patients with spontaneous hypertension.

Patients often undergo a modified nimodipine regimen, transitioning from the standard 60 mg every 4 h dosage to 30 mg every 2 h. This adjustment typically occurs in response to dose-related hypotension, a common scenario in intensive care units, reported to be as prevalent as 49% of all patients with nimodipine. However, the clinical efficacy of this fragmented regimen remains untested, despite its widespread use. The contrast between the paucity of pharmacokinetic and outcome data around this fragmented regimen and its clinical prevalence is concerning. A retrospective analysis by Sandow and colleagues demonstrated that 60% of patients on prophylactic nimodipine experienced dose reductions or discontinuation due to hypotension during the highest risk period for DCI. Interestingly, these authors demonstrated that such dose-reductions or dose-discontinuation were associated with poorer clinical outcomes. Similarly, high compliance with the enteral administration regimen of nimodipine was associated with increased odds of favourable survival and hospital discharge compared to regimens involving split doses (30 mg every 2 h) or withholding. In a prospective study of patients receiving intravenous nimodipine at 2 mg/h 66, 51% of patients experienced episodes of interrupted treatment due to

hypotension (defined as the need of >10 μg of noradrenaline for blood pressure support), with an additional 28.5% of patients having their dose reduced. This study demonstrated that interrupted or reduced regimens were associated with an increase in DCI episodes. Contrary to expectations and findings in other studies, Riva and colleagues reported that following a weight-adjusted intravenous regimen, nimodipine levels in blood were not correlated to the administered dose; whilst nimodipine levels in CSF correlated to clinical outcomes, the serum-to-CSF ratio was variable, as shown in in Table 1.

Table 1: Dose-response clinical and experimental nimodipine studies.

Author, Journal, Year	Study type	Intervention	Nimodipine dose and administration	Pharmacokinetics Nimodipine levels	Renal/Liver function	Findings
Terziivanov, D. Int J Clin Pharmacol Ther, 1999	Prospective, clinical study. Chronic renal failure patients, no SAH. (n=24).	Population PK-model applying the NPEM2 algorithm.	Day 1 study: 30 mg nimodipine tablet. Day 2 to 5 study: 30 mg enteral nimodipine Q8 h.	NPEM2 algorithm based on patients' nimodipine concentrations close to the estimated patients' Css and (NPEM2-Css.	Patient's with normal and reduced renal function. No specified GFR. Creatinine clearance: 51 to 80 and 25 to 50 ml/min. Liver function not tested.	Nimodipine disposition showed higher variability following the first dose (from 98% to 223%) than at steady state. The most variable PK data was MRT, followed by t(1/2el). Renal failure led to a higher variability on disposition parameters amongst patients with mild-moderately renal function than with advanced renal failure.
Seker F, Neuroradiology, 2013	Experimental model in rats	*Ex-vivo* isolated segments of SCA on a serotonin and PGA2 suspension.	Topical nimodipine administered at doses of 10 pM -1 μg.	N/A	N/A	Arterial vasodilation was dependant on nimodipine concentration. The vasodilatory capacity of nimodipine was lesser in spastic vessels, this was attributed to vessel wall remodelling.
Vinall PE, Stroke, 1989	Experimental case-control study in cats (n=8)	*In vitro* 1 cm section of the MCA placed in a photo-diameter gauge and bathed intraluminal and extraluminally. with an artificial Krebs-type solution.	Seven cats pre-treated with 200 μg injected into the lingual artery, (intraluminal group). Eight cats pre-treated	N/A	N/A	In control cats, 5-HT significantly reduced angiographic vessel diameter persisting for 120 min and returned to baseline in 6 h. Extraluminal and

			with 200 µg injected intracisternal, (extraluminal group).			intraluminal nimodipine produced immediate, but not significant, vasodilation.
MacKenzie M, Canadian Journal of Hospital Pharmacy, 2014	Retrospective cohort (n=166)	Standard dosing regimen *vs.* non-standard regimen (30 mg Q2 h).	60 mg enteral nimodipine Q4 h versus 30 mg enteral nimodipine Q2 h (for patients who had developed hypotension and required a dose reduction).	N/A	N/A	Half of patients were exposed to an unproven regimen. Vasospasm was associated with higher odds of receiving the non-standard regimen.
Sandow N, Neurocritical Care, 2016	Retrospective cohort (n=270)	Standard dosing regimen *vs.* non-standard regimen.	60 mg enteral nimodipine Q4 h *vs.* Dose reduction or dose discontinuation due to hypotension.	N/A	N/A	60% of all patients did not receive the standard dosing. Poor outcomes were associated with having had a reduced or discontinued dose.
Wessell A, Frontiers in Neurology, 2017	Retrospective cohort (n=118)	Standard dosing regimen with no withholding or reduced dosing *vs.* Reduced or withholding regimes. Additional: Low-dose UFH protocol.	60 mg enteral nimodipine Q4 h (17%) *vs.* Two nimodipine compliance groups: a) One dose held (78%). b) One dose split (5%)	N/A	N/A	Multivariate analysis showed that age, WFNS grade and nimodipine compliance were associated with increased odds of hospital survival with meaningful neurological outcome.
Hernandez-DuranS, World Neurosurg, 2019	Retrospective cohort (n=170)	Standard dosing regimen *vs.* Interrupted dosing	Parenteral nimodipine at 2 mg/h infusion *vs.* 60 mg enteral nimodipine Q4 h. *vs.* Nimodipine reduction *vs.* Nimodipine interruption	N/A	N/A	Nimodipine administration was discontinued in a 51% of all patients. A full-dose regimen was only observed in 20% of patients. The discontinuation of nimodipine was associated with

			when hypotension was requiring vasopressors or CPP<65 mmHg.			greater incidence of DCI.
Riva R, Clin Neuropharmacol, 2019	Prospective cohort (n=23)	Standard dosing regimen compared with arterial and CSF concentrations.	Nimodipine infusion at 1 mg/h, increased to 2 mg/h and continued to day 21. Nimodipine dose was 13 to 38 µg/kg/h.	N/A	N/A	The dose of nimodipine did not correlate with arterial or CSF nimodipine concentrations. Arterial concentrations did not correlate with CSF concentrations. Concentration of nimodipine in the CSF correlated with long-term clinical outcome.

Note: SAH: Subarachnoid Haemorrhage; PK: Pharmacokinetics; NPEM2: Non-parametric Expectation Maximization Model; Css: Steady-state concentration; GFR: Glomerular Filtration Rate; MRT: Mean Residence Time; t(1/2el): terminal elimination half-life; SCA: Superior Cerebellar Artery; PGA2: Prostaglandin A2; MCA: Middle Cerebral artery; 5-HT: Serotonin; UFH: Unfractionated Heparin; WFNS: World Federation Neurosurgical; CPP: Cerebral Perfusion Pressure; DCI: Delayed Cerebral Ischemia; CSF: Cerebrospinal Fluid.

The Newton trials compared the prophylactic effects of the conventional enteral nimodipine regimen against EG-1962, a biocompatible and bioabsorbable carrier polymer, administered intracranially. This polymer has the capacity to release nimodipine microparticles over 21 days. The Newton trial aimed to define the maximum safe and effective dose whilst bypassing its adverse effects. 68 In this trial, six dose-levels cohorts were used according to dose-limiting toxicities defined as: new increase of Intracranial Pressure (ICP), sustained hypotension, new onset of seizures, new "neuro-worsening" (as defined by CONSCIOUS investigators) and deranged liver or renal function, however, it did not show substantial differences in neurological outcomes between groups.

RESULTS AND DISCUSSION

This review explores the background and limitations on the dosing of nimodipine for patients with aneurysmal SAH. It highlights the paucity of evidence guiding the current clinical dosing practices.

As previously stated, under physiological conditions, there is a 10,000-fold gradient between extracellular and intracellular calcium concentrations. This gradient is maintained through various mechanisms, including voltage-sensitive and receptor-operated calcium channels, energy-dependant calcium extrusion mechanisms, and intracellular calcium sequestrating by organelles such as the mitochondria and the sarcoplasmic reticulum. The presence of multiple pathways regulating the intracellular calcium concentration is crucial for ensuring cellular homeostasis, but such multi-fold regulation may minimise the relevance of the specific benefit of nimodipine. Furthermore, patients' exposure to a cerebral ischemic milieu and neuro-inflammation may have been more frequent in the past when securement of the aneurysm was not prioritised; such practices could have contributed to DCI and overstated the benefit of nimodipine. However, over the past two decades, early securement of aneurysms has become standard practice, alongside interventions that increase the clearance of blood at the subarachnoid space. Therefore, it is questionable to extrapolate the benefit and dosage of nimodipine from a clinical practice that is now obsolete.

In addition to vasodilation, primarily driven by nimodipine's (-) -(S) enantiomer, the phosphodiesterase inhibitory activity through nimodipine's (+) -(R) enantiomer may be a crucial mechanism of action. The stereoselective metabolism of nimodipine is considered a potential factor in its clinical efficacy, as the most vasorelaxant enantiomers may be metabolised and eliminated faster. Thus, it remains unclear whether this could potentially impact on clinical effectiveness.

Nimodipine also displays other pharmacological effects that include the potentiation of beta-blockers, reduction of platelet aggregation (through the inhibition of platelet transmembrane calcium channels), inhibition of thromboxane, serotonin-release inhibition, and blockade of thromboxane-induced vasoconstriction; however, it remains unproven if these pathophysiological mechanisms could have a pivotal role during DCI.

Despite its favourable safety profile, well documented adverse effects such as hypotension, bradycardia, hepatitis, jaundice, and skin rash have been reported. Of particular concern are pharmacological interactions with agents that inhibit Cytochrome P450 3A4, which is the main metabolic pathway for nimodipine. Inhibition of nimodipine metabolism by these agents could lead to elevated nimodipine plasma concentrations and an increased risk of adverse effects. Examples of such agents include macrolide antibiotics, protease inhibitors, azole antimycotics, fluoxetine, valproic acid, and grapefruit. Conversely, simultaneous administration of Cytochrome P450 3A4 inducers could decrease nimodipine plasma concentrations, potentially resulting in suboptimal clinical effects. Medications in this category include carbamazepine, phenobarbital, and phenytoin. Some studies have suggested a theoretical basis for the limited clinical efficacy of nimodipine when co-administered with phenytoin, raising important considerations given that many of the original clinical trials upon which the current practice stands, used phenytoin for the treatment or prophylaxis of SAH-related seizures. These interactions underscore the importance of carefully monitoring patients receiving nimodipine therapy, especially when co-administered with drugs that affect its metabolism.

In addition, epigenetics may play an important role in the variability of nimodipine's plasma concentrations across populations with distinct characteristics. A recent pharmacokinetic study highlighted the potential impact of genetic polymorphisms on nimodipine metabolism, demonstrating differences in C_{max} and AUC of nimodipine between homozygous-CYP3A5 and heterozygous individuals.

A recent review on the pharmacokinetics of nimodipine has also remarked the paucity of data regarding nimodipine blood concentrations and outcomes, but there are substantial differences between such review and the current one. First, our review focusses on the current dosing of nimodipine, emphasizing on the fact of how original individualised dosing has emerged into a standardised dosing and how this practice reflects a lack of adjustment to patients' physiology. Furthermore, in the current review, we hypothesise that standardised dosing may have negative implications in therapeutics and outcomes. Conversely, the review by Mahmoud and colleagues' centres on the pharmacokinetics of nimodipine across populations of diverse physiology.

Second, our review extends on the concept of DCI and how its multifactorial aetiology affects the purpose for which nimodipine was tested. This is currently a pivotal issue, as angiographic vasospasm is no longer at the core of the potential complications following SAH, therefore the prophylactic role of nimodipine may have become diluted.

Third, with DCI being multifactorial and independent of angiographic vasospasm, a prophylactic target following SAH becomes difficult to define. Therefore, in the absence of a clear prophylactic goal, the establishment of a therapeutic blood level for nimodipine is not plausible. This is currently, a major limitation on the standardised use of nimodipine and a challenge for future studies.

Current unresolved issues and potential pathways for improvement

Several aspects regarding the use of nimodipine remain unclear and unresolved. Firstly, the substitution of the terminology "vasospasm" with DCI introduces ambiguity into the outcome measure, given the multifactorial nature of DCI. In this context of unclear clinical target, defining a therapeutic plasma level of nimodipine becomes challenging due to the lack of specific treatment goals. Without an established therapeutic plasma level, our capacity to define optimal dosing for nimodipine is limited.

Furthermore, it has been observed that patients with SAH who are intubated and receive enteral nimodipine through a feeding tube tend to exhibit lower plasma levels and reduced bioavailability. This subgroup often comprises patients with a deteriorated level of consciousness and those with more severe clinical grading. Although a causal relation has not been established, the potential inadequacy of nimodipine dosing in these patients remains unconfirmed.

The reduced bioavailability of nimodipine when administered with food could impact its clinical effectiveness. Moreover, there are notable gaps in recommendation within published guidelines, reflecting the paucity of data on this subject. Addressing these gaps through further research is crucial for optimising nimodipine therapy and improving patient outcomes.

Non-evidence-based enteral regimens of nimodipine are common in clinical practice. Regimens such as administering 30 mg doses of nimodipine every 2 h due to systemic hypotension, as well as the discontinuation of enteral dosing, have been associated to worse clinical outcomes.

The current dosing regimen is standardised regardless of factors such as weight, renal function, and liver clearance, which limits the ability to optimise dosing for specific subgroups. Consequently, the potential for prophylactic failure due to underdosing or adverse effects resulting from overdosing has not been evaluated in clinical trials.

CONCLUSION

The considerable variability in nimodipine's pharmacokinetics may result in suboptimal dosing for many SAH patients. A re-evaluation of the standardised dosing regimen of nimodipine and the consideration of a potential benefit of individualised dosing regimens are warranted.

AUTHORS' CONTRIBUTIONS

Conceptualization: JB and JP. Data curation: JB and JP. Visualization and writing-original draft: JB. Writing-review editing: JB, MPHM, JR, KBL and CY. The manuscript complies with all instructions to authors. All authors have read and approved the submitted manuscript; the manuscript has not been submitted elsewhere, nor published elsewhere in whole or in part.

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