Article published online: 2025-05-26

Unraveling NAGMA: A Case Series of Intravenous Nimodipine-Induced Metabolic Acidosis in Neuro-ICU Patients

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Asian J Neurosurg 2025;20:805–809.

Abstract

Nimodipine, a calcium channel blocker of the dihydropyridine class, is used prophylactically in ruptured aneurysmal subarachnoid hemorrhage (aSAH) patients to reduce the incidence of poor outcome, delayed cerebral ischemia, and delayed ischemic neurological deficits. This case series reports nine instances of normal anion gap metabolic acidosis (NAGMA) in patients with aSAH following intravenous nimodipine administration in a neuro-intensive care unit (NICU) over 2 months. The patients, aged 4 to 68 years (seven male, two female), presented with acute headaches and were diagnosed with intracranial aneurysms, managed with aneurysmal clipping or coiling. Intravenous nimodipine (1–2 mg/hour) was initiated as per protocol, along with standard NICU care. After 48 to 72 hours, patients developed hyperventilation, respiratory alkalosis, and a significant decrease in bicarbonate, leading to NAGMA. Despite ruling out common causes like gastrointestinal losses and nephrotoxic drugs, renal tubular acidosis was suspected. The NAGMA resolved spontaneously 6 to 7 days postsurgery, coinciding with the discontinuation of intravenous nimodipine. A retrospective audit revealed a common factor: using a specific brand of intravenous nimodipine, a new arrival from the hospital supply. This phenomenon was later corroborated in a similar case from another hospital. The case highlights the importance of pharmacovigilance, postmarketing surveillance, and regulatory oversight in identifying rare drug-related adverse events, particularly in high-acuity settings like NICU.

Keywords
- NAGMA (normal anion gap metabolic acidosis)
- nimodipine
- adverse drug events
- pharmacovigilance
- aneurysmal subarachnoid hemorrhage

article published online
May 26, 2025

DOI https://doi.org/10.1055/s-0045-1809355.
ISSN 2248-9614.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Nimodipine, a calcium channel blocker of the dihydropyridine class, is used prophylactically in ruptured aneurysmal subarachnoid hemorrhage (aSAH) patients to reduce the incidence of poor outcome, delayed cerebral ischemia, and delayed ischemic neurological deficits. Both oral and intravenous routes of nimodipine are available.[1] Some of the reported complications of nimodipine usage were hemodynamic instability like hypotension, bradycardia, refractory vasoplegia, and worsening pulmonary function.[2–4] In our case, we found an unusual side effect of intravenous nimodipine used for aSAH treatment: normal anion gap metabolic acidosis (NAGMA). We have done a thorough literature search where we could not find any reports of NAGMA due to intravenous nimodipine, and we are presenting these drug-related new adverse events of case series in aSAH cases.

Case Report

After obtaining informed and written consent from all the patients, we are presenting a series of nine unusual cases of normal anion gap metabolic acidosis (NAGMA) in our neurointensive care unit (NICU) due to intravenous nimodipine usage in aSAH patients over a short span of 2 month (►**Table 1**). The cases belonged to the extremes of age (4–68 years), with six being male and two being female. All the patients presented with acute severe headaches, and noncontrast computer tomography revealed a subarachnoid hemorrhage. Consequently, all patients were evaluated for the source of the bleeding using diagnostic digital substation angiography (DSA). All patients were diagnosed with intracranial aneurysms: seven patients had anterior circulation aneurysms, while one pediatric patient had a posterior circulation aneurysm. We managed all patients in the NICU. According to our institutional protocol, we initiated intravenous infusion of nimodipine 1 to 2 mg/hour,[5] along with antipyretic, proton-pump blockers, antiepileptic, cerebral decongestant, and antibiotics during the intervention, while maintaining normotension and euvolemia. The intravenous fluids used for all patients were balanced isotonic crystalloids. The baseline blood investigation and arterial blood gas (ABG) analysis were unremarkable. Most of the patients ($n = 6$) underwent early (within 24 hours of ictus) aneurysmal clipping, while two patients received coiling under DSA. In the postoperative period, days 0 and 1, the patient was clinically stable and planned for extubation. However, after 48 to 72 hours, the patient started hyperventilating (increase in tidal volume [TV] and respiratory rate [RR]). ABG analysis showed carbon dioxide washout and a significant decrease in bicarbonate level with metabolic acidosis. However, the urine output was normal, with urea and creatinine within normal range and no signs of acute kidney injury. After 72 hours, persistent metabolic acidosis, rising chloride, and falling potassium levels resulted in NAGMA. After ruling out the gastrointestinal causes[6] (diarrhea, nasogastric aspirates, fistula) and common drugs[7] (topiramate, acetazolamide), we concluded renal tubular acidosis with a hypokalemic variant for the cause of NAGMA in these cases.[8] We initiated continuous sodium bicarbonate via infusions to rapidly alleviate acidosis' effect on intracranial pressure and started potassium correction with an infusion of potassium chloride.[9] Furthermore, we avoided nephrotoxic drugs and maintained mean arterial pressure between 70 and 80. Initially, we suspected DSA contrast agent induced and changed the contrast agent to isotonic, but NAGMA persisted.

Notably, there were no episodes of NAGMA in patients undergoing DSA in cath lab for procedures other than aneurysms. Even though the patient's sensorium was good, a large TV with increased RR due to NAGMA caused the patient to be on a high dose of sedation, protracted mechanical ventilation, prolonged NICU stay, and increased ventilator-associated pneumonia incidence and morbidity. Two cases also got reintubated due to this. Two cases were tracheostomized due to prolonged ventilation with decreased sensorium. However, this NAGMA spontaneously resolved 6 to 7 days after the surgical procedure. Upon careful retrospective evaluation and audit, we identified a commonality among all these patients: the intravenous nimodipine that all the patients received on admission to the NICU as per institutional protocol and the drug brand, which was a new arrival from the hospital supply. Although the drug was available under different marketing brand names, the manufacturer was the same (►**Fig. 1**). Per institutional protocol on day 5 of the acute phase, the nimodipine was switched from intravenous to oral.[10] This led to a spontaneous resolution of NAGMA, even though the drug label of the intravenous formulation mentioned only nimodipine and water for injection (no preservatives).

On a recent day, we were contacted by our colleague working in an NICU from another state hospital for a similar case in which a 43-year-old male was diagnosed with a ruptured anterior communicating artery aneurysm by DSA and was intubated because of decreased Glasgow Coma Scale ($E_2V_2M_5$). The next day morning, surgical clipping was done and mechanically ventilated because of preoperative decreased sensorium. He was also started on intravenous nimodipine in the postoperative period, and the patient's trachea was extubated after 24 hours but got reintubated within 24 hours because of increased RR and severe carbon dioxide washout ($PaCO_2$- 15 mm Hg). At this time, we received a call for suggestions. On enquiring, we came to know that the same manufacturer (►**Fig. 1**) of intravenous nimodipine was used, but with a different brand name, so we immediately asked to stop, and NAGMA existed and managed similarly to our cases. However, the patient was tracheostomized earlier to decrease the length of NICU stay and financial burden. In the next 48 hours, the patient was weaned from the ventilator and discharged with Glasgow Coma Scale $E_4V_TM_6$.

Discussion

The case series highlights an unusual and previously unreported side effect of intravenous nimodipine usage in

Table 1 Patient demographic distribution and important parameters

Parameters	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case8	Case 9
Age (y)	55	25	60	68	66	46	55	4	43
Gender	M	M	F	F	M	M	M	M	M
Admission date	1/7/24	3/7/24	2/7/24	3/7/24	13/7/24	20/7/24	23/7/24	26/7/24	16/11/24
Diagnosis	Anterior communicating artery aneurysm	Posterior communicating artery aneurysm	Anterior communicating artery aneurysm	Posterior communicating artery aneurysm	Anterior communicating artery aneurysm	Right middle cerebral artery aneurysm	Right middle cerebral artery aneurysm	Basilar top aneurysm	Anterior communicating artery aneurysm
Date of ictus	30/6/24	1/7/24	29/6/24	3/7/24	10/7/24	14/7/24	18/7/24	24/7/24	14/11/24
MHH	IV	II	II	II	III	III	II	II	III
MF	III	II	II	III	III	III	III	IV	IV
Admission GCS	E1VtM3	E4V5M6	E4V5M6	E4V5M6	E4V5M6d	E4V5M6	E4V5M6	E4V5M6	E3V2M5
Comorbidities	HTN DM	–	–	–	HTN	HTN	HTN DM	–	–
Day of DSA done from admission	2	0	1	1	0	1	2	0	0
Procedure done	Clipping	Clipping	Clipping	Clipping	Coiling	Clipping	Clipping	Coiling	Clipping
Day of coiling/ clipping from admission	11	1	2	1	0	1	4	0	0
Day of IV nimodipine from admission	1	0	0	0	0	0	4	0	2
Day of increase in TV and RR from admission	3	2	3	2	2	3	6	2	4
Day of NAGMA from admission	3	3	3	2	3	4	6	2	5
NaHCO3 infusion	+	–	–	+	–	–	+	–	+
Change of IV to tablet nimodipine days from admission	7	6	5	6	7	5	10	5	6
Sedation	+	+	+	+	+	+	+	–	–
Vasopressor	+	–	–	–	–	+	–	–	–
Tracheostomy	+	–	–	–	–	+	–	–	+
Reintubation	–	–	–	–	–	+	+	–	+
Date of discharge	2/8/24	15/7/24	11/7/24	15/7/24	3/7/24	7/8/24	8/8/24	3/8/24	26/11/24
GCS at discharge	E3VtM3	15	15	15	15	E4VtM6	15	15	E3VtM5

Abbreviations: DM, diabetic mellitus; DSA, digital substation angiography; E, eye; F, female; GCS, Glasgow Coma Scale; HTN, hypertension; IV, intravenous; M, male; MF, modified Fisher; MHH, modified Hunt and Hess; M, motor; NAGMA, normal anion gap metabolic acidosis; NaHCO3, sodium bicarbonate; RR, respiratory rate; t, tracheostomized; TV, tidal volume; V, verbal.

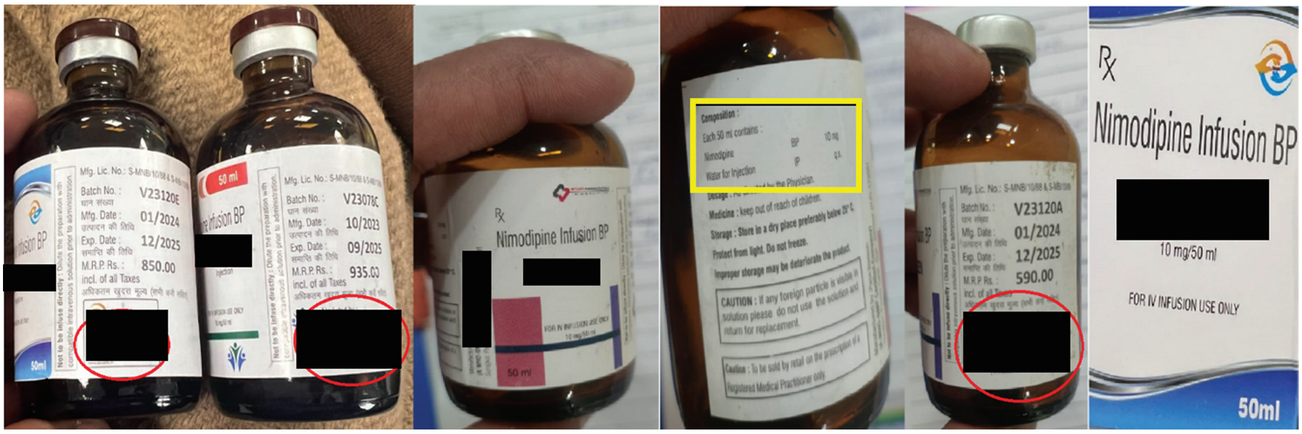

Fig. 1 Showing intravenous (IV) nimodipine vials available under different brand names and marketed by different companies but with a common manufacturer and all the vials showing the composition of nimodipine only without any preservatives (yellow box).

patients with aSAH. While nimodipine is routinely used in aSAH management to reduce the incidence of delayed cerebral ischemia and improve neurological outcomes, this series identifies NAGMA as a potential adverse effect, particularly associated with a specific manufacturer of intravenous nimodipine.

In our cohort of nine patients, all of whom developed NAGMA within 48 to 72 hours of receiving intravenous nimodipine, we observed typical metabolic acidosis signs, including hyperventilation and a decrease in bicarbonate levels, without evidence of acute kidney injury. The condition was managed by correcting electrolyte imbalances with sodium bicarbonate and potassium infusions and discontinuing intravenous nimodipine, which led to the acidosis' resolution in most cases. The common factor in all these cases was the specific formulation of intravenous nimodipine, which was newly introduced in our hospital.

The absence of NAGMA in other patients who received the DSA contrast agents or underwent similar procedures but did not receive the intravenous nimodipine formulation strongly suggests a causal link between the drug and the metabolic disturbance. Additionally, NAGMA resolved spontaneously after switching from intravenous to oral nimodipine, further supporting this hypothesis.

We do not know the exact reason. However, some impurities or manufacturing defects may have led to NAGMA in our case series, which needs to be addressed as an adverse postmarketing event. While we cannot definitively conclude that nimodipine is the sole cause of NAGMA in all cases, this series underscores the importance of careful monitoring of adverse drug reactions, especially in intensive care settings where patients are on multiple medications. The findings raise concerns about potential differences in formulations of nimodipine and the need for further investigation into the specific ingredients or manufacturing processes that may contribute to such adverse effects.

This case series calls on clinicians to remain vigilant when administering intravenous nimodipine and to report any unusual or severe side effects for further study. Furthermore, it emphasizes the need for postmarketing surveillance to detect and manage emerging drug-related complications, ensuring patient safety and optimal therapeutic outcomes.

Conclusion

As a priority, we would like to present these case series for the attention of all our intensivists. After ruling out all the possible causes, we conclude that manufacturing defects due to impurities or preparation methods may be the most probable cause of this intravenous nimodipine complication from a particular manufacturer. The case series highlights the importance of pharmacovigilance and spontaneous reporting of postmarketing adverse events and regulatory oversight.

Note
The manuscript has been read and approved by all the authors, the requirements for authorship, as stated earlier in this document, have been met, and each author believes that the manuscript represents honest work.

Authors' Contributions
All authors contributed equally to the article and have fulfilled various criteria qualifying them for inclusion in the authors' list. Their contributions span multiple key areas of the research and manuscript development process. All authors contributed to the concepts, design, definition of intellectual content, literature search, clinical and experimental studies, data acquisition, data analysis, statistical analysis, and manuscript preparation. In addition to these, they also took part in manuscript editing and manuscript review. K.G. is the guarantor for the manuscript. These contributions reflect substantial involvement by each author across multiple stages of the study and publication process, thereby justifying their authorship in accordance with standard publishing guidelines.

Conflict of Interest
None declared.

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