Case Report

DOI: 10.7860/JCDR/2026/88532.24026

Intravenous Nimodipine Associated Severe Metabolic Acidosis and Haemodynamic Collapse in patient with Aneurysmal Subarachnoid Haemorrhage: A Case Report

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ABSTRACT

Nimodipine is a dihydropyridine Calcium Channel Blocker (CCB) routinely used in the management of aneurysmal Subarachnoid Haemorrhage (aSAH) to prevent Delayed Cerebral Ischemia (DCI). While oral route of administration is the standard of care, intravenous (i.v.) nimodipine is occasionally used in critically ill patients. However, i.v. administration may lead to profound hypotension and uncommon metabolic derangements. A 54-year-old hypertensive female presented with aSAH secondary to ruptured left anterior communicating artery aneurysm. Following aneurysm clipping, the patient was monitored in ICU with standard neurocritical care and oral nimodipine. The patient was transitioned to i.v. nimodipine due to high clinical suspicion of cerebral vasospasm and DCI. Within 48 hours of i.v. nimodipine, the patient developed severe hypotension requiring high-dose vasopressor support, mixed metabolic acidosis, hyperchloremia, ketonemia, and hyperglycaemia. Workup for sepsis, postsurgical meningoencephalitis, and other causes was inconclusive. An adverse drug reaction related to i.v. nimodipine was suspected. Discontinuation of nimodipine and targeted metabolic support led to improvement of clinical symptoms. This case highlights the rare but potentially life-threatening adverse effects of i.v. nimodipine, including refractory hypotension and severe metabolic acidosis. Clinicians should exercise caution, maintain close monitoring, and consider drug-induced toxicity when unexplained metabolic and haemodynamic instability occurs. The present case emphasises that vigilant haemodynamic and metabolic monitoring during i.v. nimodipine therapy is essential.

Keywords: Calcium channel blockers, Cerebral ischemia, Cerebral vasospasm, Drug toxicity, Ketoacidosis

CASE REPORT

A 54-year-old female presented to the emergency department with a sudden-onset severe headache (VAS 9/10) associated with multiple episodes of vomiting, of four hours duration. There was no history of loss of consciousness, seizures, photophobia, or aura. She had a known history of hypertension but was not on regular antihypertensive medications (no prior medications), and had no known Diabetes Mellitus (DM).

Initial evaluation showed stable vitals and no focal neurological deficits, GCS E3V4M6, moving all four limbs. Initial routine blood investigations were within normal limits. Two-dimensional echocardiography revealed a Left Ventricular Ejection Fraction (LVEF) of 60% with mild concentric Left Ventricular Hypertrophy (LVH), likely related to her hypertensive state; no wall motion abnormalities, Grade 1 left ventricular diastolic dysfunction and trivial mitral regurgitation and tricuspid regurgitation was noted. Non-contrast CT brain followed by CT cerebral angiography revealed a SAH with cerebral oedema, mild hydrocephalus and ruptured left anterior communicating artery aneurysm.

The patient underwent left frontal craniotomy, aneurysmal clipping, and External Ventricular Drain (EVD) placement. Postoperatively, standard neuroprotective care was initiated, including oral nimodipine (60 mg every 4 hours via Ryles tube), antiepileptics (Levetiracetam 500 mg i.v. every 12th hourly), and hydration. Blood pressure was supported with low-dose noradrenaline {target Systolic Blood Pressure (SBP) 160-170 mmHg and MAP 110 mmHg} in line with institutional vasospasm prevention protocols. The patient was extubated on Postoperative Day (POD) 1 with GCS E3V3M5 with mild right upper limb weakness (power 4/5). The EVD was removed on POD 2; CT imaging remained satisfactory.

On POD 3, worsening of right upper limb weakness (power 3/5) and a mild drop in GCS to E2V2M5 was noted. CT brain showed no new findings. Suspecting DCI, oral nimodipine was switched to i.v. infusion at 2 mg/hr. Within 48 hours of initiating i.v. nimodipine, persistent hypotension requiring escalating noradrenaline (up to 2.0 µg/kg/min), fever, and hyperventilation were noted. ABG showed severe mixed metabolic acidosis (pH 7.09, HCO_3 8.5 mmol/L, lactate 3.76 mmol/L, chloride 115 mmol/L, Anion Gap (AG) 23.5 mmol/L, delta AG 11.5 mmol/L, gap-to-gap ratio 0.74). Serum glucose was 279 mg/dL; blood ketones were elevated (5.4 mmol/L), and urine ketones were 3+ positive, HbA1C was 6.0%. The detailed description of ABG parameters is depicted in [Table/Fig-1]. The CT image findings are depicted in [Table/Fig-2].

Inflammatory markers (CRP 88.1 mg/L, procalcitonin 0.05 ng/mL), blood cultures, and lumbar puncture were inconclusive. Sepsis, and adrenal insufficiency were considered but ruled out. A probable adverse drug reaction related to i.v. nimodipine with stress-induced ketotic metabolic acidosis was considered.

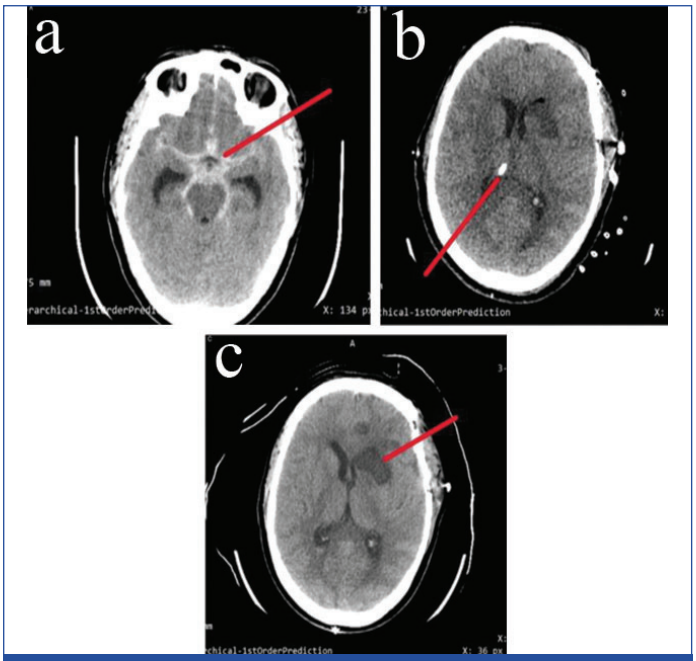
The i.v. nimodipine was stopped immediately. The patient was treated with calcium gluconate infusion, 50% Dextrose infusion with insulin infusion (0.1 U/kg/hr), and isotonic bicarbonate solution. Calcium supplementation was initiated to counteract calcium channel blockade-related myocardial and vascular depression. Over the next 24-48 hours, the acidosis corrected, lactate levels normalised, and vasopressor requirements reduced [Table/Fig-1,3]. The patient was tracheostomised and continued to recover neurologically (GCS E3V4M6), though the subsequent hospital course was complicated by hospital-acquired infections. The patient was later decannulated and discharged with GCS E4V4M6 with mild right upper limb weakness.

DISCUSSION

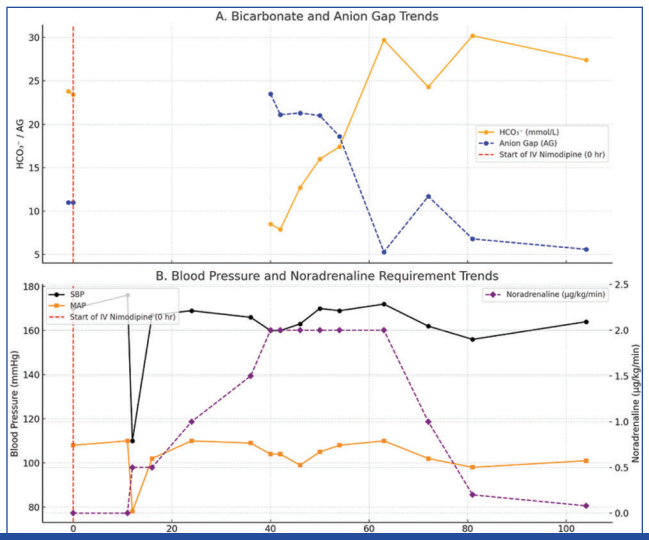
Nimodipine, a dihydropyridine calcium channel blocker, mitigates cerebral vasospasm in patients with aSAH and helps in the

ABG Parameters	Baseline	Time frame after starting i.v. Nimodipine infusion (hours)														
		0 h	11 h	12 h	16 h	24 h	36 h	40 h	42 h	46 h	50 h	54 h	63 h	72 h	81 h	104 h
pH	7.41	NM	NM	NM	NM	NM	NM	7.09	7.32	7.4	7.46	7.45	7.40	7.51	7.5	7.5
PaO_2 (mmHg)	102	NM	NM	NM	NM	NM	NM	198	154	141	164	163	91.4	108	139	84
$PaCO_2$ (mmHg)	37	NM	NM	NM	NM	NM	NM	28.7	15.5	21	22.6	25.3	48.2	31	38.8	32.4
HCO_3 (mmol/L)	23.4	NM	NM	NM	NM	NM	NM	8.5	7.9	12.7	16.0	17.4	29.7	24.3	30.2	27.4
Chloride (mmol/L)	109	NM	NM	NM	NM	NM	NM	115	120	121	120	120	121	116	112	108
Sodium (mmol/L)	144	NM	NM	NM	NM	NM	NM	147	149	156	157	156	157	152	149	141
Lactate (mmol/L)	0.97	NM	NM	NM	NM	NM	NM	3.76	3.4	4.81	3.55	2.78	2.26	1.91	1.8	1.08
AG (mmol/L)	11	NM	NM	NM	NM	NM	NM	23.5	21.1	21.3	21.0	18.6	5.3	11.7	6.8	5.6
SBP (mmHg)	170	176	110	167	169	166	160	160	163	170	169	172	162	156	164	170
DBP (mmHg)	79	75	70	77	74	72	80	77	60	72	75	80	80	76	75	88
MAP (mmHg)	108	110	78	102	110	109	104	104	99	105	108	110	102	98	101	109
HR (bpm)	78	82	90	92	90	92	108	110	106	103	108	96	84	75	72	92
Noradrenaline (µg/kg/min)	0	0	0.5	0.5	1	1.5	2.0	2.0	2.0	2.0	2.0	2.0	1	0.2	0.08	0

[Table/Fig-1]: Time frame of haemodynamic parameters and ABG trend after starting i.v. nimodipine infusion.
AG: Anion gap; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; HR: Heart rate, PaO_2: Partial pressure of arterial oxygen; $PaCO_2$: Partial pressure of arterial carbon dioxide; HCO_3: Bicarbonate; *NM: Not measured- ABG had worsening almost after 40 hrs of starting Nimodipine and hence values from 40 hrs are considered for evaluation of toxicity



[Table/Fig-2]: Non-contrast Computed Tomography (NCCT) brain images demonstrating temporal evolution of aSAH. a) Acute aSAH with hyperdensities in the basal cisterns and sylvian fissures; b) Postoperative image following External Ventricular Drain (EVD) placement and craniotomy showing decompressed ventricles with residual intraventricular haemorrhage; c) Follow-up scan on Postoperative Day (POD) 12 demonstrating resolution of haemorrhage with residual parenchymal hypodensities.



[Table/Fig-3]: Line Graph showing trends of ABG: a) haemodynamic parameters and Noradrenaline requirements; b) after starting i.v. Nimodipine infusion.

prevention of DCI [1,2]. The 2023 AHA/ASA guidelines explicitly recommend early initiation of enteral nimodipine as the standard of care for preventing DCI and improving functional outcomes after aSAH, underscoring that the oral route should be preferred whenever clinically feasible [3]. Oral administration is preferred due to its favourable pharmacokinetics and reduced risk of systemic hypotension [4,5]. However, the oral bioavailability of nimodipine is highly variable, ranging from only 3-30%, owing to extensive hepatic first-pass metabolism via the CYP3A4 system [6]. In critically ill patients with aSAH, this variability is further compounded by impaired gastrointestinal motility, nausea, vomiting, and altered hepatic function - all of which reduce enteral drug absorption unpredictably [6]. A multicenter retrospective cohort study by Mahmoud SH et al., demonstrated that different enteral nimodipine formulations and administration techniques through feeding tubes may not be bioequivalent, with certain methods associated with higher rates of DCI, further highlighting the absorption unreliability that drives clinicians toward i.v. administration in high-acuity settings [7]. The i.v. nimodipine, by bypassing first-pass hepatic metabolism entirely, achieves significantly higher and more consistent plasma and CSF concentrations compared to the oral route [8]; however, this markedly increased systemic bioavailability is precisely what amplifies the risk of adverse haemodynamic and metabolic effects [4,5]. The i.v. nimodipine is considered in patients unable to tolerate enteral medications or in cases of suspected worsening vasospasm and DCI, but can lead to haemodynamic instability due to its potent systemic vasodilatory effects. Göttsche J et al., observed that i.v. nimodipine at 2 mg/hr should be reserved for higher-grade aSAH patients or those with compromised enteral absorption, and that switching back to oral should be pursued as soon as clinically viable - a principle that, in the present case, was not applied early enough [9].

The present case highlights not only severe hypotension but also profound metabolic acidosis following i.v. nimodipine. The switch to i.v. nimodipine was temporally associated with a cascade of systemic effects - refractory hypotension, severe metabolic acidosis, ketosis, and neurologic deterioration. The metabolic acidosis was multifactorial: a mixed picture comprising a non-AG component (hyperchloremia, gap-to-gap ratio 0.74) alongside a high AG component (AG 23.5 mmol/L) driven by lactic acidosis and ketonemia - a combination not previously described in the context of i.v. nimodipine toxicity. Importantly, there was no prior history of diabetes or previous episodes suggestive of diabetic ketoacidosis. The HbA1C of 6.0% indicated a prediabetic state, predisposing to stress-induced ketoacidosis. Studies in critically ill non-diabetic patients have shown that prediabetes markedly increases the risk

of stress-induced hyperglycaemia with reported rates of 61.1% in prediabetic versus 6.6% in non-prediabetic patients (Fisher's exact test, $p < 0.05$), corresponding to an approximately nine-fold higher risk which may predispose such patients to ketoacidosis under conditions of physiological stress. [10,11]. A large retrospective review of nearly 50,000 CCB exposures reported to US poison centers by Brenner MA et al., found that hyperglycaemia, though present in only 1.2% of cases, was associated with a 21.8-fold increased relative risk of a severe medical outcome - establishing hyperglycaemia as a critical prognostic marker of CCB toxicity severity [11]. The present patient's serum glucose of 279 mg/dL and blood ketones of 5.4 mmol/L are fully consistent with this toxidrome.

The underlying pathophysiology of the observed metabolic derangements is likely multifactorial. At standard therapeutic doses, dihydropyridines selectively block L-type calcium channels in peripheral vascular smooth muscle, producing vasodilation; however, at elevated systemic concentrations - as occurs when i.v. administration bypasses first-pass hepatic metabolism - pharmacological selectivity is lost, and L-type channels in the myocardium and pancreatic beta-cells are also blocked. Mitochondrial dysfunction secondary to intracellular calcium channel blockade impairs oxidative phosphorylation and ATP hydrolysis, directly contributing to lactate production and metabolic acidosis. Simultaneously, blockade of pancreatic beta-cell L-type calcium channels suppresses insulin secretion, producing hypoinsulinemia and end-organ insulin resistance, which manifest as hyperglycaemia [11]. Systemic vasodilation from i.v. nimodipine leads to tissue hypoperfusion and further lactate accumulation. Stress-induced hyperglycaemia with relative insulin resistance in the prediabetic patient precipitated ketosis. Additionally, hyperchloremia from concurrent isotonic saline resuscitation, exacerbated by bicarbonate loss, contributed to the non-AG component of the metabolic acidosis. i.v. nimodipine bypasses hepatic first-pass metabolism, markedly increasing systemic exposure and thereby amplifying all of these toxic effects [5].

The pharmacokinetic profile of nimodipine is directly relevant to understanding why i.v. infusion predisposes to toxicity. The terminal elimination half-life is approximately 8-9 hours, but initial elimination is rapid (equivalent to a 1-2-hour half-life), necessitating frequent dosing by the oral route; by contrast, continuous i.v. infusion maintains sustained high systemic concentrations without the troughs seen with intermittent oral dosing. With approximately 95% plasma protein binding and a volume of distribution ranging from 0.94 to 2.46 L/kg, nimodipine accumulates significantly in tissue compartments, and its hepatic CYP3A4 metabolism is bypassed entirely during i.v. infusion [6]. This combination of high protein binding, large volume of distribution, and continuous systemic delivery without first-pass attenuation creates conditions for progressive drug accumulation and concentration-dependent toxicity- particularly in patients with underlying metabolic vulnerability such as the prediabetic state present in this case. These pharmacokinetic considerations also explain the temporal course observed: toxicity manifested within 48 hours of initiating i.v. infusion, consistent with the time required for drug accumulation to reach tissue-level concentrations sufficient to produce non-selective multi-channel blockade.

Similar cases of i.v. nimodipine-associated toxicity [12,13] have been reported in the literature, though predominantly describing isolated hypotension or Normal Anion Gap Metabolic Acidosis (NAGMA) rather than the combined High Anion Gap Metabolic Acidosis (HAGMA)- NAGMA-ketonemia pattern observed here. A recent case series by Manyam U et al., reported nine cases of NAGMA following i.v. nimodipine infusions for aSAH in the neuro-ICU over a two-month period. Retrospective audit identified a common specific manufacturer's batch as the likely causative factor, attributing the metabolic derangement to formulation-related impurities or preparation methods rather than the i.v. route per se [12]. Lodha S et al., described a case of single-dose calcium channel blocker-associated severe hypotension and metabolic lactic acidosis in a patient with end-stage liver disease, underscoring how impaired CYP450-mediated drug metabolism- whether from intrinsic hepatic dysfunction or i.v.-route-related bypass of first-pass extraction- dramatically amplifies CCB toxicity risk [13]. The present case differs meaningfully from both: the proposed mechanism is primarily route-dependent, with i.v. administration bypassing first-pass metabolism producing excess systemic drug exposure rather than a batch-specific formulation issue or hepatic dysfunction. Moreover, the metabolic derangement was more complex, involving HAGMA in addition to NAGMA, with significant ketonemia - a pattern not described in any prior reported case involving i.v. nimodipine. The US FDA has issued a black-box warning against i.v. administration of nimodipine capsule contents; however, purpose-formulated i.v. nimodipine solutions continue to be used in neurocritical care internationally, including in India, Europe, and China [8,9].

The management of CCB toxicity in the present case followed established principles. Calcium gluconate infusion was initiated to reverse calcium channel blockade-related myocardial and vascular depression. Insulin-dextrose therapy was administered at 0.1 U/kg/hr with 50% Dextrose infusion, analogous to Hyperinsulinemic-Euglycaemic Therapy (HIET). HIET is now recognised as a cornerstone of CCB toxicity management, with published case series reporting success rates of 80.4-100% [14]. The rationale is that CCB toxicity shifts myocardial substrate preference away from free fatty acids toward carbohydrates, and insulin reverses the impaired glucose uptake, insulin resistance, and hypoinsulinemia resulting from pancreatic beta-cell channel blockade [14]. Mégarbane B (2023) has further argued that high-dose insulin should be initiated before or alongside vasopressors in CCB toxicity, given its direct inotropic and metabolic benefits that vasopressors alone cannot replicate [15]. In the present case, the combination of calcium supplementation, insulin-dextrose, isotonic bicarbonate, and prompt discontinuation of i.v. nimodipine resulted in progressive normalisation of acid-base parameters and vasopressor weaning over 24-48 hours - consistent with the expected temporal response to removal of the offending agent and targeted metabolic resuscitation. Using the Naranjo adverse drug reaction probability scale, the association between i.v. nimodipine and the observed haemodynamic and metabolic derangements was classified as probable (score=7), supported by the temporal relationship between drug initiation and toxicity onset, the absence of an alternative explanation after thorough workup, and prompt recovery following drug discontinuation. Monitoring for early signs of toxicity including hypotension, acidosis, and neurologic worsening is crucial. Oral nimodipine remains the preferred route when clinically feasible [3,4].

CONCLUSION(S)

This case underscores a rare but potentially life-threatening complication of i.v. nimodipine- severe refractory hypotension and mixed metabolic acidosis comprising both high AG and non-AG components, with associated ketonemia in a prediabetic patient. Clinicians managing aSAH in the neurocritical care setting should maintain a high index of suspicion for i.v. nimodipine toxicity when unexplained haemodynamic instability or metabolic acidosis develops during therapy. Prompt discontinuation of the offending drug, combined with targeted metabolic resuscitation including calcium supplementation, insulin-dextrose infusion, and bicarbonate therapy can lead to full haemodynamic recovery. Vigilant monitoring of haemodynamic and metabolic parameters is essential during i.v. nimodipine infusion, and oral nimodipine should be reinstated as soon as clinically feasible. Further pharmacovigilance and

prospective studies are needed to better characterise the incidence and mechanisms of i.v. nimodipine-associated metabolic complications.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Mar 30, 2026
- Manual Googling: May 16, 2026
- iThenticate Software: May 19, 2026 (1%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Feb 24, 2026**
Date of Peer Review: **Apr 24, 2026**
Date of Acceptance: **May 21, 2026**
Date of Publishing: **Aug 01, 2026**