Association Between Acute Colonic Pseudo-Obstruction (Ogilvie Syndrome) And Nimodipine Use. Case Series And Comprehensive Review

Orlando De Jesus (drodejesus@aol.com)
University of Puerto Rico Medical Sciences Campus: Universidad de Puerto Rico Recinto de Ciencias Medicas
José Sánchez Jiménez
University of Puerto Rico
Juan C. Vicenty
University of Puerto Rico

Research Article

Keywords: aneurysm, colon, nimodipine, pseudo-obstruction, subarachnoid hemorrhage

DOI: https://doi.org/10.21203/rs.3.rs-756411/v1

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Abstract

Background:

Nimodipine is a calcium channel blocker indicated for the management of patients with aneurysmal subarachnoid hemorrhage (SAH). Oral nimodipine has rarely been implicated in the development of acute colonic pseudo-obstruction in patients treated for SAH. Nimodipine acts by inhibiting the transmembrane influx of calcium ions essential for the excitation-contraction coupling process of smooth muscle cells. We thought that its mechanism of action could predispose patients to develop acute colonic pseudo-obstruction (Ogilvie syndrome). The purpose of this study was to revise the existing literature concerning the association between acute colonic pseudo-obstruction and nimodipine use in patients with SAH.

Methods:

Two patients with aneurysmal SAH who received oral nimodipine and developed Ogilvie syndrome were discussed. All previously published cases of aneurysmal SAH associated with acute colonic pseudo-obstruction were reviewed.

Conclusion:

This report linking the oral use of nimodipine with Ogilvie syndrome may further support the association of this disease with nimodipine use during the treatment of patients with aneurysmal SAH.

Introduction

Ogilvie syndrome, also known as acute colonic pseudo-obstruction, is the distention of the colon caused by decreased motility in the absence of mechanical obstruction [1, 5, 25]. The most common risk factors associated with its development include severe infection, severe disease process, myocardial infarction, congestive heart failure, surgical procedures, metabolic disorders, electrolyte disorders, renal insufficiency, systemic lupus erythematosus, gastrointestinal carcinoma, severe trauma, spinal cord injury, cerebral stroke, Guillain-Barre, Parkinson disease, some medications, and alcohol abuse.

Nimodipine, a second-generation dihydropyridine type calcium channel antagonist that blocks the influx of extracellular calcium through L-type, voltage-gated calcium channels, is indicated to manage patients with aneurysmal SAH. Nimodipine is considered a safe drug with only minor side effects, including a minimal drop of the systemic blood pressure or reversible increases in the liver enzymes [13, 18, 29, 31]. Very rarely, nimodipine had been associated with the development of acute colonic pseudo-obstruction. This report presented two patients who had aneurysmal SAH and developed acute colonic pseudo-obstruction while receiving oral nimodipine. The available literature was reviewed to determine the possible association between nimodipine use in aneurysmal SAH and Ogilvie syndrome.

Case 1:
**Presentation:** A 61 year/old female with a BMI of 32.6 kg/m² and a history of hypertension not using the prescribed medication for the last four years presented to the local health center after a sudden severe worst headache. She was alert and oriented with mild neck rigidity. A head computed tomographic (CT) scan showed a SAH and was intubated due to the findings before being transferred to our institution. On arrival at our institution, she had a blood pressure of 174/97 mm Hg with a Glasgow coma scale (GCS) of 10 intubated. A repeat head CT scan showed a moderate diffuse cisternal SAH with a small amount of intraventricular hemorrhage. The patient was started on oral nimodipine 60 mg orally every 4 hours and a stool softener (docusate calcium 240 mg daily). A cerebral digital subtraction angiogram (DSA) was performed the next morning, which showed a small anterior communicating aneurysm filling primarily through the left side. During the procedure, she was embolized with the complete occlusion of the aneurysm and then transferred to the intensive care unit and extubated. Post extubation, the patient had a GCS of 15.

**Investigations:** Two days after admission, her abdomen was distended, and a kidney, ureter, and bladder (KUB) X-ray film showed a distended large bowel. She was tolerating diet and passing gas and stools; however, the distention persisted for the next two days. An abdominal CT scan showed a 10 cm dilatation of the ascending and transverse colon with mildly dilated jejunal loops. At this time, it was suspected that she had developed acute colonic pseudo-obstruction. By this day, she had been on nimodipine for four days.

**Treatment:** The diet was suspended, and a nasogastric tube was placed with intermittent suction for five days; however, the distention did not improve. Neostigmine 2 mg was given intravenously over 3 to 5 minutes and repeated the next day. Atropine was available at the bedside but not required. A brain CT angiography showed moderate vasospasm with a 50% reduction in the diameter of the anterior cerebral vessels. Although asymptomatic, she had been five days without nimodipine; therefore, it was restarted given the possibility of delayed ischemic complications. A repeat abdominal CT scan was performed, which showed interval reduction of the dilatation, now 7 cm at the ascending and transverse colon with a normal descending colon, sigmoid, and rectum. Diet was restarted two days later, but she had significant abdominal distention, so the diet was again stopped. A repeat cerebral DSA showed no evidence of vasospasm. It was decided not to continue the nimodipine as she was already close to 21 days post hemorrhage. As the distention had not improved, a colonoscopy for decompression was attempted, but decompression was unachieved; thus, a rectal tube was placed with an output of 850 ml in 24 hours. The abdominal distention decreased, and the tube was removed the next day, and the diet was restarted.

**Outcome:** A KUB X-ray performed six days later showed resolution of the colon distention. The patient was discharged five days after the rectal tube was removed, and 28 days after the initiation of the pseudo-obstruction.

**Case 2:**
**Presentation:** A 46 year/old female with a BMI of 26.8 kg/m2 and a history of bipolar disease and heart arrhythmias with a pacemaker had a sudden severe headache and arrived at our emergency department for evaluation. Neurological examination showed a GCS 15. The head CT scan showed a small anterior interhemispheric SAH, and the CT angiography showed an anterior communicating artery aneurysm. The patient was started on oral nimodipine 60 mg orally every 4 hours and a stool softener (docusate calcium 240 mg daily). A cerebral DSA was performed the next morning, which confirmed the presence of an anterior communicating artery aneurysm filling primarily through the left side. She was taken to the operating room for a craniotomy and clipping of the aneurysm. Just after the opening of the dura mater, the patient had an episode of rebleeding. A ventriculostomy was placed, which relaxed the brain, and the aneurysm was successfully clipped. Postoperative, she remained alert and oriented. The head CT scan the next morning showed an increased amount of SAH.

**Investigations:** Five days after admission, she developed a distended abdomen, and a KUB X-ray film showed a distended large bowel. She was tolerating diet and passing gas and stools; however, the distention persisted. The next day, an abdominal CT scan showed an 8 cm dilatation of the ascending and transverse colon. At this time, it was suspected that she developed acute colonic pseudo-obstruction. By this day, she had been using nimodipine for nine days.

**Treatment:** Diet was immediately stopped, and a nasogastric tube was placed with intermittent suction. However, the distention did not improve, and a rectal tube was placed two days later with a large output in 24 hours. The abdominal distention noticeable decreased. The tube was removed the next day and started again on a diet. Nimodipine was restarted to complete the 21 days of treatment.

**Outcome:** During the following days, the KUB X-ray showed progressive reduction of the distention of the colon, and the patient was discharged seven days after the rectal tube was removed and twelve days after the initiation of the pseudo-obstruction. Six months later, a ventriculoperitoneal shunt was placed because of the development of hydrocephalus.

**Discussion**

In the early 1980s, nimodipine was considered the drug of choice for preventing and treating cerebral vasospasm following SAH due to its preferential cerebrovascular action [2,3,4,22,26]. It is now recognized that oral nimodipine improves the clinical outcome in patients with delayed cerebral ischemia after SAH secondary to intracranial arterial spasm [10,24,26,27]. Nimodipine blocks the influx of extracellular calcium. The transmembrane influx of calcium ions is essential for the excitation-contraction coupling process of smooth muscle cells. Specific antagonists of this calcium influx can therefore inhibit smooth muscle contraction without regard to the exciting stimulus. Experimental evidence of inhibitory effects of calcium antagonists on intestinal smooth muscle contraction had been previously published [7,17,21,33]. These experimental data provided evidence that calcium antagonists exert inhibitory effects on the gastrointestinal tract due to their intrinsic mechanism of action. It has been demonstrated that nifedipine
inhibits humans’ colonic electric spike activity induced by eating [21]. Side effects such as abdominal pain or constipation may occur in patients treated with oral nimodipine for extended periods [12,23,30].

In 1948, Ogilvie reported two patients with signs of colonic obstruction in the absence of any organic disease of the colon [25]. He attributed its development to the interruption of the sympathetic supply to the large intestine. However, after surgical exploration, both patients were found to have disseminated abdominal metastatic disease. Ogilvie syndrome is now recognized as a colonic pseudo-obstruction caused by decreased motility in the absence of mechanical obstruction; still, the eponym was attributed to his idea of the interruption of the sympathetic supply. Ogilvie syndrome is associated with a 25-30% mortality in severe cases, which increases to 50% if the patient develops ischemia and perforation [19]. Early recognition and management are essential. The specific pathophysiology of acute colonic pseudo-obstruction is still unclear. It may include many etiologies, risk factors, pathological conditions, and multiple associations leading to altered autonomic regulation of colonic motility [8,34]. Excessive parasympathetic suppression, sympathetic stimulation, or both are thought to produce an imbalance in the colonic autonomic innervation. All these factors produce temporary suppression of intestinal motility, inducing acute dilatation of the colon. Nimodipine has rarely been associated with the development of Ogilvie syndrome in aneurysmal SAH. In this report, we presented two cases in which its use could have been associated with the development of acute colonic pseudo-obstruction.

In 1984, Bullock and Thomas were the first to report acute colonic pseudo-obstruction in patients with a SAH [6]. Their series included two such cases; however, there is no description if nimodipine was used. Nimodipine was probably not used in those two cases as it was approved for medical use in 1985. In 1987, Torrealba et al were the first to describe a patient with acute colonic pseudo-obstruction who received intravenous nimodipine for a SAH whose condition improved after a rectal tube was inserted and the nimodipine was discontinued [32]. However, no cerebral aneurysm was identified in the angiographic studies. Hund et al. reported in 1990 a similar complication after the use of intravenous nimodipine in a patient with SAH secondary to an aneurysm of the anterior communicating artery [15]. They also mentioned four previous cases of SAH in which the patients developed abdominal distention after intravenous nimodipine.

Fahy described in 1996 a case of pseudo-obstruction of the colon in a patient receiving oral nimodipine therapy for a SAH secondary to an aneurysm of the posterior communicating artery [11]. This report was the first to associate the oral use of nimodipine with the development of Ogilvie syndrome. They continued treatment with nimodipine for the recommended time, despite the colonic dilatation, as they thought the risk of removing the medication was more detrimental than its continuation. The pseudo-obstruction was ultimately resolved after endoscopic colon decompression and rectal tube placement. In one of our patients, we also implemented similar measures to improve the pseudo-obstruction. Our other patient required a rectal tube after an unsuccessful colonoscopy.

Patients with Ogilvie syndrome are initially managed with supportive therapy for decompression of the gastrointestinal tract, including gastric and rectal tubes. Among the conservative treatments,
discontinuation of the oral intake, placement of a nasogastric tube for proximal gut decompression, correction of fluid and electrolyte abnormalities, treatment of any underlying concomitant illnesses, and the cessation of medications such as narcotics and anticholinergics that adversely affect colonic motility had been effective [16]. Those who do not respond within 1-2 days may require neostigmine use. The use of intravenous neostigmine, an acetylcholinesterase inhibitor, is the best-documented pharmacological treatment for acute colonic pseudo-obstruction with initial response rates of 60-90% [8,16,20,28]. Although neostigmine has a short elimination half-life, most patients in the study by Ponec et al. achieved a sustained response after the initial dose [28]. We had to use neostigmine in one of our patients; however, its use only partially improved the distention, reappearing when the patient was started again on a diet. Haj et al. reported similar outcomes using conservative management or interventional management to manage Ogilvie syndrome [14]. Patients who are refractory to treatment should receive endoscopic decompression [19]. Colonoscopic decompression is successful in approximately 80% of patients. Exploratory laparotomy is limited to those patients in whom complications occur [9].

**Conclusion**

Even though the cause and mechanism of acute colonic pseudo-obstruction are not yet clearly understood, calcium channel blockers may predispose patients to develop the condition. Our two cases and prior reported cases provide additional evidence about the possible causal relation between nimodipine use and Ogilvie syndrome in patients treated for aneurysmal SAH. The continued use of nimodipine after the development of the acute colonic pseudo-obstruction had not been established, and each physician should decide based on the risk of withdrawing the medication. Our data suggest that further investigation of the impact of oral nimodipine on the gastrointestinal tract of aneurysmal SAH patients is justified.

**Abbreviations**

SAH = subarachnoid hemorrhage
CT = computed tomographic
GCS = Glasgow coma scale
DSA = digital subtraction angiogram
KUB = kidney, ureter, and bladder

**Declarations**

**Funding:** No funding was received to assist with the preparation of this manuscript.
Conflict of interest: The authors have no conflicts of interest to declare relevant to this article’s content. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Availability of data and material: Not applicable in this study type (review)

Code availability: Not applicable in this study type (review)

Ethics approval: There are no patient identifiers in this publication. The University Institutional Review Board verified the manuscript and allowed its submission and publication.

Consent to participate: Informed verbal consent was obtained from both individual participants included in the study.

Consent for publication: The participants have consented to the submission of the review manuscript to the journal. No photography is included in the study.

Author’s contributions:

Concept and design: Orlando De Jesus, José Sánchez Jiménez, MD

Data acquisition: Orlando De Jesus, José Sánchez Jiménez, MD, Juan C. Vicenty

Drafting the manuscript: Orlando De Jesus, José Sánchez Jiménez, MD, Juan C. Vicenty

Revising the manuscript: Orlando De Jesus, José Sánchez Jiménez, MD, Juan C. Vicenty

Approval of the final manuscript: Orlando De Jesus, José Sánchez Jiménez, MD, Juan C. Vicenty

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