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ABSTRACT

Nimodipine is a drug belonging to the group of calcium channel blockers, very well tolerated, widely recognized for its central action as a vasodilator preventing vasospasm secondary to aneurysmal subarachnoid haemorrhage. It is currently approved as a drug used in the treatment of this type of haemorrhage, mainly because it is effective in reducing neurological deficits due to delayed cerebral ischemia. In addition, due to its relaxing action on the cerebral vascular musculature and its facility to cross the blood-brain barrier, it has multiple functions in other types of cerebral vascular lesions such as ischemic stroke and other neurological conditions involving stress or cell death. Its role as a prophylactic agent in the treatment of migraine and its effect as a neuroprotective agent have also been evaluated.

Keywords
nimodipine,
aneurysmal subarachnoid
haemorrhage,
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INTRODUCTION

Calcium channel blockers act by blocking the entry of calcium ions into vascular and cardiac smooth muscle cells during membrane depolarization. Its inhibition causes essentially relaxation of arterial vessels, because muscle contraction is highly dependent on calcium influx. This is why the main effects of calcium channel blockers are relaxation of arterial and vascular smooth muscle cells, resulting in arterial vasodilatation [1]. In general, they are indicated in the treatment of hypertension and other major cardiovascular disorders; however, their use has also been suggested in the management of cognitive disorders and other neurological disorders [2].

Based on the above, the pharmacological effect of vasodilators on cerebral blood flow, such as calcium channel blockers, has been extensively studied and evaluated in different pathological conditions that compromise cerebral vascular integrity. Nimodipine, being lipophilic, can cross the blood-brain barrier; in fact, studies have shown that nimodipine is more lipophilic than nifedipine and its volume of distribution in the brain of rats was three times greater than that of nifedipine [3].

Early pharmacological studies characterized nimodipine as a potent cerebral vasodilator drug [3]. Subsequently, several studies confirmed the cerebral vasodilator activity of nimodipine and mentioned that, in addition to its calcium antagonist action on the smooth muscle of cerebral blood vessels, nimodipine may have direct neuronal effects [3]. Thus, different studies were developed to identify its efficacy in different brain alterations that generate some degree of compromise in the cerebral vascular endothelium, such as traumatic brain injury, stroke and migrainea.

One of the main complications following a subarachnoid hemorrhagic stroke is arterial spasm, which is caused by the presence of blood in the subarachnoid space [4]. Nimodipine plays an important role in inhibiting reflex vasospasm, thus acting as a neuroprotector. It has also been shown that the prophylactic use of nimodipine in patients with aneurysmal subarachnoid hemorrhage reduces the risk of ischemic brain damage, a frequent complication of this event [5,6]. In this review, the essential aspects of nimodipine for the management of patients in the neurocritical state are presented.

PHARMACOLOGICAL ASPECTS OF NIMODIPINE

Nimodipine (C21-H26-N2-O7) is a drug belonging to the group of second-generation 1,4-dihydropyridine calcium channel blockers [7]. It has been used for various situations since the 1980s, where it was initially implemented in the management of systemic arterial hypertension but later approved by the Food and Drug Administration (FDA) for the treatment of vasospasm after aneurysmal subarachnoid haemorrhage [7-9]. It is not widely used, since its use is mainly aimed at the management of patients with this type of stroke [10].

Mechanism of action

Voltage-dependent calcium channels (VDCCs) are widely distributed throughout the body and their function is to regulate the excitability and secretion of different cell types. Nimodipine binds to the alpha-1 subunits containing the voltage sensor and transmembrane pores of L-type VDCCs, acting as a negative allosteric modulator of the function of this channel [7,8]. Four alpha-1 isoforms have been identified within the L-type class of which Cav1.2 or Cav1.3 are those that are widely expressed in the cardiovascular system and in neurons, therefore, they are of great importance in the pathophysiology of the central nervous system (CNS), because they have a high relationship with cells involved in the regulation of the neurovascular unit [8].

During depolarization of the smooth muscle cells of blood vessels, there is an influx of calcium ions; nimodipine acts by blocking these channels, preventing this influx and causing vasodilatation [7]. In addition, it has a high lipid solubility, so it has a preference for acting on cerebral blood vessels and can cross the blood-brain barrier [7,10]. In this way, it has an effect on cerebral blood flow by having the ability to reverse the persistent pathological activation of L-type channels in cerebral arteries, which are responsible for reflex vasoconstriction in case of injury [8,11].

CLINICAL UTILITY OF NIMODIPINE IN NEUROCRITICAL CARE

Haemorrhagic stroke

Nimodipine is an FDA-approved drug included in the general treatment of aneurysmal subarachnoid haemorrhage (aSAH) [12,13]. It has the ability to reduce the risk of cerebral ischemia and improves clinical prognosis. The dose recommended by clinical practice guidelines is 60 mg orally every 4 hours

during the first 48 hours after the onset of symptoms or when the patient's hemodynamic status permits, and is maintained for the following 21 days [12,14]. If the enteral route cannot be used, it is recommended to use intravenous nimodipine, gradually increasing up to 2mg/h, avoiding arterial hypotension; it should be switched to the oral route as soon as possible [12].

The most frequent complication of aSAH is delayed cerebral ischemia, which is believed to be the product of multiple processes such as angiopathic micro- and macrovasospasm, loss of autoregulation, cortical depolarization, microthromboembolism, and heterogeneity of capillary transit time [8,15,16]. It has been postulated that cortical depolarization propagates from the nucleus and vulnerable regions, causing additional ischemia both adjacent to the core lesion and in distant regions with compromised perfusion due to large vessel vasospasm; when nimodipine is used, cortical depolarization is initiated less frequently and less severely, decreasing the risk of delayed cerebral ischemia [8].

Several studies have demonstrated the efficacy of nimodipine in improving neurological status following this type of hemorrhagic event [17,18]. Philippon *et al* [19] conducted a prospective randomized double blind study in patients with aSAH to determine whether the use of nimodipine reduces the severity of ischemic deficits secondary to vasospasm and found that, although not observed in all cases, nimodipine effectively decreases the occurrence of neurological deficits due to vasospasm. Pickard *et al* [20] conducted a prospective trial with the aim of establishing the effect of nimodipine on the incidence of ischemic events and proven cerebral infarction, and on the reduction of death and severe disability after subarachnoid hemorrhage; it was shown that the use of oral nimodipine 60 mg every four hours is well tolerated, reduces cerebral infarction and improves outcome after subarachnoid hemorrhage. Finally, in a similar study, Petruk *et al* [21] concluded that treatment with nimodipine in poor-grade patients with subarachnoid hemorrhage results in an increase in the number of good outcomes and a reduction in the incidence of delayed neurologic deterioration due to vasospasm.

The efficacy of nimodipine in the context of subarachnoid hemorrhage has also been evaluated

in children. Song *et al* [22] conducted a prospective randomized controlled clinical trial in children with subarachnoid hemorrhage, with the aim of evaluating the effect of prophylactic nimodipine in preventing vasospasm and improving outcomes in this type of patient. As a result, they concluded that prophylactic nimodipine cannot reduce the incidence of vasospasm in children with subarachnoid hemorrhage, but may improve short-term brain function

On the other hand, Sriganesh *et al* [23] evaluated the effect of intra-arterial nimodipine on regional cerebral oxygen saturation (rSO₂) and systemic hemodynamic indices during therapy for cerebral vasospasm following aSAH. Analysis of the results showed that there was no change from baseline in ipsilateral and contralateral rSO₂ after administration of intra-arterial nimodipine, but there was a significant decrease in mean arterial pressure and total peripheral resistance index. These latter hemodynamic changes could offset any potential effect of intra-arterial nimodipine to improve rSO₂. Further studies are needed to corroborate this theory

Several studies have also been conducted comparing the effectiveness of nimodipine with other calcium channel blockers in the treatment of patients with aSAH. One of these is the study by Schmid-Elsaesser *et al* [24] where they evaluated the efficacy of magnesium (nature's physiological calcium antagonist) versus nimodipine to prevent delayed ischemic deficits after aSAH. They showed that, in the magnesium group, 15% experienced clinical vasospasm and 38% experienced angiographic/transcranial Doppler vasospasm, compared to 27% and 33% of patients in the nimodipine group, respectively [24]. The authors conclude that the efficacy of magnesium in the prevention of delayed ischemic neurological deficits in patients with aSAH is comparable to that of nimodipine and further studies are needed to better define its role in these neurological circumstances and on its combined administration with nimodipine.

Ischemic stroke

Most strokes are ischemic, i.e., caused by reduced blood flow with obstruction of small and large vessels. This sudden loss of blood supply is associated with a massive influx of calcium ions into neurons, which is the common pathway leading to

cell death [25]. It is proposed that inhibition of calcium entry by the use of calcium channel blockers could protect neurons and reduce neurological deterioration after stroke

Several studies have investigated the efficacy of nimodipine in improving clinical outcomes after ischemic stroke. Steen et al [26] conducted a study in pigtailed monkeys, which were subjected to 17 minutes of complete cerebral ischemia followed by 96 hours of intensive care treatment. They evidenced that the neurological outcome at 96 hours after ischemia was significantly better in nimodipine-treated monkeys than in controls, and a histopathological scoring system yielded a significantly better mean score for the treated group than for the untreated group [26].

In the randomized, double-blind, multicenter clinical trial conducted by The American Nimodipine Study Group, a positive finding was that patients treated with nimodipine had a 30% reduction in the frequency of clinical worsening compared to placebo within 18 hours after stroke [27].

However, the results compared with those of other clinical trials are contradictory. In the study by Kaste et al [28], where the hypothesis that nimodipine would improve functional outcome in acute hemispheric ischemic stroke was tested, no differences in functional outcome were observed between treatment groups. Similarly, in a Cochrane meta-analysis where randomized controlled trials comparing a calcium antagonist versus a control in people with acute ischemic stroke were included, it was found that calcium antagonists showed no effect on the primary outcome (RR 1.05; 95% CI: 0.98 to 1.13) or on death at the end of follow-up (RR 1.07, 95% CI 0.98 to 1.17); therefore, the authors concluded that no evidence was found to support the use of calcium antagonists in patients with acute ischemic stroke [29]. Further studies are needed to clarify whether the use of nimodipine in ischemic stroke is beneficial or not.

Uses of nimodipine in other neurological conditions

Calcium channel antagonists, such as flunarizine, are used as a drug for migraine prophylaxis, so the role of nimodipine in the treatment of this condition has been studied [30]. Nimodipine could intervene in the pathophysiology of migraine by blocking the entry of calcium into the smooth muscle cells of cerebral

vessels, preventing the vasomotor manifestations of migraine. The possibility of a neurogenic mechanism of action has also been studied [31].

Recent case reports have elucidated the efficacy of nimodipine in the treatment of prolonged hemiplegic migraine (HM) linked to the ATP1A2 gene mutation [32]. The case was reported by Dannenberg et al [32] where a girl diagnosed with MH developed drowsiness, confusion, nausea, vomiting, photophobia, left hemiparesis and unilateral central facial palsy, after two days of headache. Initially, levetiracetam and dexamethasone were administered, but due to the persistence of symptoms, nimodipine was added on the sixth day to prevent new spasms [32]. Nimodipine infusion rapidly improved the patient's symptoms and was well tolerated, and within 12 hours improved left arm motor function. The authors concluded that nimodipine treatment should be considered for prolonged migraine attacks in patients with ATP1A2 mutations.

On the other hand, clinical and experimental data have attributed a neuroprotective effect to calcium channel blockers, specifically nimodipine. This is why Leisz et al [33] conducted a study with the aim of evaluating the relationship of nimodipine treatment on the *in vitro* neurotoxicity of various cell types subjected to stress. Schwann cell lines, neuronal cells and astrocytes were treated for 24 hours with nimodipine and incubated under osmotic, oxidative and heat stress conditions. The results demonstrated a cell type-independent protective effect of prophylactic treatment with nimodipine, through decreased activation of caspase 3 and 7, and increased activation of CREB (cyclic adenosine monophosphate response element-binding protein) and AKT (protein kinase B) signaling. The authors suggest that these investigations should be continued *in vivo* to determine whether these mechanisms can be transferred to patient tissues.

Similarly, Herzfeld et al [34] analyzed the neuroprotective effects of nimodipine on Neuro2a neuroblastoma cells after the application of cell death inducers (surgery-associated stress, such as heat or mechanical stress). The results indicated that nimodipine significantly decreased ethanol-induced cell death by up to 9% at all concentrations tested; in addition, heat-induced cell death was reduced by 2.5% and mechanical treatment-induced cell death was reduced by up to 15%. These findings

demonstrated that nimodipine rescues Neuro2a cells from stress in a mild but significant manner,

ADVERSE EFFECTS AND LIMITATIONS OF USE OF NIMODIPINE

Nimodipine is generally well tolerated, but its use is correlated with some side effects related to its vasodilator property. Hypotension is the most frequently reported adverse effect compared to placebo treatment [35]. Hajizadeh *et al* [36] conducted a study with the aim of determining adherence to oral nimodipine administration in patients admitted with aSAH. They found that 39% of patients who started nimodipine in the neurosciences intensive care unit reduced the dose due to excessive falls in blood pressure, and transient discontinuation occurred in 2% patients [36]. They concluded that most patients with aSAH did not complete 21 days of nimodipine and hypotension was the main reason for the change or suspension of the dose. However, the hypotensive effect can be minimized by generating control of the blood pressure by reducing the dose given to the patient.

Other adverse effects of the drug include headache, dizziness, flushing, nausea, diarrhea, edema of the feet, rash and palpitations. An increase in serum liver enzyme concentrations has also been reported in patients on intravenous treatment with nimodipine, but it is reversible and is thought to be due to the ethanol in the intravenous formulation and not to nimodipine [35]. Isolated cases of confusion with psychosis and myocardial ischemia during treatment with nimodipine have been reported [35].

Intrathecal administration of dihydropyridines has been suggested with the aim of decreasing Cerebrospinal Fluid (CSF) concentrations of these drugs, with lower systemic concentrations and fewer systemic side effects, mainly hypotension [37]. Etminan *et al* [37] reviewed data from intrathecal application of a slow-release nimodipine EG-1962 microparticle system to improve outcome and prevent delayed cerebral ischemia following subarachnoid hemorrhage. Given the strong rationale for investigating the effects of EG-1962 in patients suffering from subarachnoid hemorrhage, they initiated two clinical trials on intracisternal and intraventricular application of EG-1962.

Hänggi *et al* [38] also described the development of sustained-release nimodipine microparticles that

can be administered directly into the subarachnoid space or brain ventricles to improve the outcome of patients with aSAH. Eight injectable formulations of nimodipine microparticles in poly (DL-lactide-co-glycolide) (PLGA) polymers were tested *in vitro*. Their efficacy has been tested and it has been concluded that Nimodipine-PLGA microparticles significantly attenuate angiographic vasospasm.

Among the contraindications, a history of hypersensitivity reaction to nimodipine is an absolute contraindication, while hepatic insufficiency and hypotension are relative contraindications for its administration. Finally, it is relevant to mention that nimodipine is not safe during pregnancy (category C) and should only be used in these circumstances if there is a strong risk-benefit ratio; breastfeeding is also contraindicated while taking the drug due to possible harmful effects on the baby [1].

FINAL RECOMMENDATIONS

The efficacy of nimodipine in improving outcomes in the treatment of aneurysmal subarachnoid hemorrhage is well established in the literature. Its pharmacological approach is aimed at reducing the harmful effects of subarachnoid blood, prevent aneurysm rebleeding, and treatment to reduce the risk of delayed cerebral ischemia or vasospasm [39]. It would be interesting to further investigate the mechanisms by which nimodipine decreases aSAH-associated complications and whether it has any impact on neurological conditions following the occurrence of the event

It is also important to investigate the effects of nimodipine on ischemic strokes, which constitute a large percentage of the events encompassed within the context of acute neurological pathology. As noted above, there is much controversy regarding the possible effects of nimodipine in the management of patients with ischemic stroke and it is essential to clarify these concepts. Likewise, future scientific research should be directed to investigate the action of nimodipine not only at the level of the cerebral vasculature, but also in the central nervous system as a whole, since it has been mentioned about the possible neuroprotective effects in other neurological pathologies.

Finally, further research is needed on microparticulate systems that have a sustained release formulation of nimodipine administered directly into the central nervous system by various

routes, such as intraventricular, which have been tested in patients with subarachnoid hemorrhage [40]. It is necessary to establish whether this method of local administration could be more beneficial than the oral presentation of nimodipine, since with the latter the concentrations administered to the vulnerable brain may be very low due to side effects such as systemic hypotension.

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