Neurocrit Care
https://doi.org/10.1007/s12028-023-01914-y

NEUROCRITICAL CARE SOCIETY

NEUROCRITICAL CARE THROUGH HISTORY

The Laboratory Origins of Nimodipine in Cerebral Vasospasm

Eelco F. M. Wijdicks*

© 2024 Springer Science+Business Media, LLC, part of Springer Nature and Neurocritical Care Society

Before calcium channel blockers were considered in randomized prospective clinical trials, investigators discovered in experimental studies that calcium antagonists, such as nimodipine, had a moderate vasodilatory effect [1, 2]. Nimodipine therefore became an interesting study drug for its potential to reduce cerebral infarction after subarachnoid hemorrhage (SAH) caused by cerebral vasospasm. When primates were studied, nimodipine reduced neither the severity of the vasospasm nor the incidence, but when given to rats before occlusion of a cerebral artery, it markedly attenuated the size of the infarcts. Therefore, it was postulated that the mechanisms leading to micro vasospasm formation, and subsequent reduction of cortical perfusion may involve L-type Ca2 + channels.

Most experimental work on calcium antagonists can be credited to George Allen and his colleagues from the Department of Neurosurgery at the University of Minnesota Medical School [3, 4]. His initial experiment showed that canine basilar and middle cerebral artery segments gave dose-dependent contractions to a variety of agents, including serotonin, prostaglandin, epinephrine and norepinephrine, histamine, and potassium cerebrospinal fluid taken from patients several days after an SAH, would cause significant contraction of large cerebral arteries. Most contractile activity was due to serotonin in the cerebrospinal fluid, but serotonin antagonists at low concentrations were not as effective in inhibiting the serotonin-induced contraction of large cerebral arteries. Additional experiments demonstrated that the removal of calcium from the bath buffer also prevented most of the contraction, which led to use of calcium antagonists. The ability of nifedipine to block the calcium-induced contractions of the basilar artery was consistent with its being an inhibitor of the influx of extracellular calcium in the basilar artery. On a molecular basis, nifedipine is an extremely sensitive inhibitor of serotonin-induced contractions of the basilar artery. The concentration of nifedipine necessary to reverse a maximal serotonin contraction is less by a factor of ten than the serotonin concentration required for the contraction (Fig. 1). In dogs, subarachnoid injection of blood produced cerebral vasospasm. Sublingual nifedipine reversed both acute and chronic vasospasm and even prevented it when administered preemptively. In cats, intravenous administration of nimodipine produced 25% dilatation of the pial arteries more prominently in small arteries. Unfortunately, high doses of intravenous nimodipine caused marked decreased in blood pressure [5].

Furthermore, they found that [3H]-nimodipine did bind frontal cortex and that the binding site was regulated by calcium [6]. Topically applied nimodipine during clipping of an aneurysm also caused visible vasodilation, but mostly in smaller arteriolar vessels [7]. Subsequently, in vivo experiments in dogs demonstrated angiographically that the subarachnoid injection of blood produced cerebral arterial spasm both immediately after the injection of blood and 2 days later. The sublingual administration of nifedipine reversed both the acute and the delayed cerebral arterial spasm. In addition, sublingual administration of nifedipine 20 min before the subarachnoid injection of blood prevented the acute spasm [3]. Skeptics noted that comparable results were reported with other drugs that relax cerebral arteries in vitro (all of which seem to interfere with calcium movement across the cell membrane). These include sodium nitroprusside, cocaine, theophylline, isoproterenol, and verapamil. "Except for the convenience of sublingual administration, there is no conclusive

*Correspondence: wijde@mayo.edu
Neurocritical Care Services, Saint Marys Hospital, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Springer

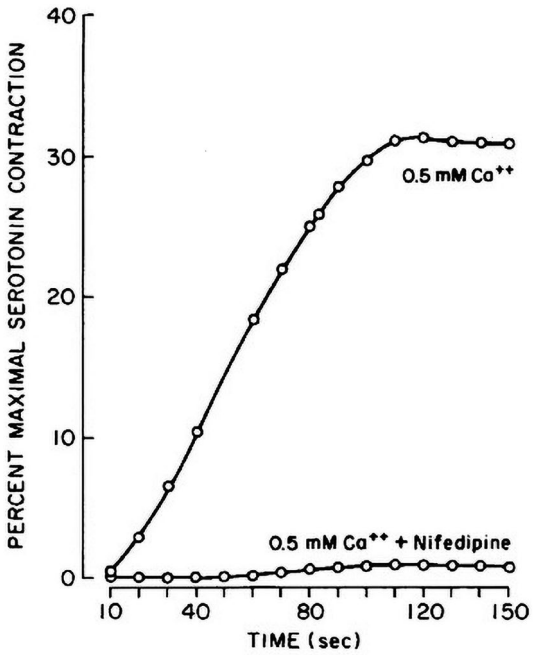

FIG. 3. Graph showing the time course of change in the resting state of contraction of one canine basilar artery after the addition of 0.5 mM Ca^{++} to a Ca^{++}-free bath in the presence and absence of 3×10^{-6} M nifedipine. This response was reproducible in three separate preparations.

Fig. 1 Canine basilar artery caliber change with use of nifedipine, used with permission from *Journal of Neurosurgery* Publishing Group

evidence that nifedipine has much more to offer than these others (all of which looked promising in animal experiments). Further human trials will determine if hypotension can be avoided at effective doses" [3].

With these data, Allen and his collaborators thought there was sufficient underpinning for a large-scale clinical trial, and they published the very first clinical trial. The first study, performed by Allen et al. [8] in 1983, suggested that nimodipine could affect outcome, but the trial was small and largely a selection of patients with cerebral ischemia from cerebral vasospasm. The trial investigators were also interested in examining whether nimodipine could have an effect on cerebral infarction due to causes other than vasospasm. Allen et al. [8] enrolled 125 patients with cerebral aneurysm during the first 96 h of their SAH. The study found that at 21 days of treatment, 8 of 60 patients given placebo and 1 of 56 patients given nimodipine had a deficit from cerebral arterial spasm. Side effects were not noted. The study also remarkably found that a large amount of subarachnoid blood on computed tomography (CT) scan did not work against the effect of nimodipine, but this negative effect was present in placebo-treated patients.

Six years later, British neurosurgeons Pickard and colleagues [9] studied a much larger group of 554 patients recruited in 3 years from multiple British centers. This study confirmed Allen's study that oral nimodipine, 60 mg every 4 h, was well tolerated and reduced cerebral infarction. In addition, outcome was better in treated patients. The benefit of nimodipine, however, was relatively small, reducing cerebral infarction on CT scan from 33 to 22%. However, poor outcome was reduced by 40% (poor outcome in 20% of nimodipine-treated patients and 33% in patients given a placebo). The Pickard study noted reduction in blood pressure with the use of nimodipine but reported no adverse effects [9].

Allen remained convinced that serotonin was the main vasoactive agent responsible for the contraction of cerebral arteries following a ruptured aneurysm. He reasoned as follows. First, there is normally almost no free serotonin in the blood because platelets actively take up any free circulating serotonin and store it in their dense granules. When the aneurysm ruptures, platelets enter the subarachnoid space. There will be a release of serotonin from the platelets and other chemicals into the cerebrospinal fluid–blood mixture. The released free serotonin remaining in basal cisterns is again actively taken up by the platelets. Thus, within a brief time after the hemorrhage, there is no significant free serotonin in contact with the 5-HT serotonin receptors of the arterial smooth muscle cells. This accounts for the lack of spasm on the initial angiogram taken within 3 days of the hemorrhage. Circulating platelets have a half-life of 4 to 5 days. If this half-life is not changed by their escape into the basal cistern, then half of the platelets will have disintegrated 4 to 5 days after the hemorrhage.

Oral nimodipine has become a standard treatment in aneurysmal SAH. Nimodipine may block calcium influx and act on smaller perforating cerebral arteries rather than larger calibers. Transcranial Doppler and angiography have never found a significant difference between nimodipine-treated patients and placebo-treated patients. Nimodipine may also reduce the severity of infarct by reducing size and by increasing fibrinolytic activity decreasing microthrombi. Briefly, there was interest in using nimodipine intraarterially because of its potent vasodilatory effect [10]. But intraarterial nimodipine did show improvement on CT perfusion scan.

Wolf et al. [10] recently demonstrated the ability of nimodipine to block calcium in a small mice study. Male C57Bl/6 N mice were subjected to SAH using the middle cerebral artery perforation model. Six hours after SAH induction, a cranial window was prepared, and the diameter of cortical microvessels was assessed in vivo by 2-photon-microscopy before, during, and after nimodipine application. **N**imodipine reduced the formation of micro vasospasm. L-type Ca2+channels

may be involved in the pathophysiology of micro vasospasm formation [11].

A Cochrane review supports the oral administration of nimodipine 60 mg every 4 h for 21 days after aneurysmal SAH [12]. Current use of nimodipine in aneurysmal SAH is difficult to implement in clinical settings given the hemodynamic instability of these patients, and these problems are still with us today [13]. Less than half of patients with aneurysmal SAH with nimodipine received the full daily dose of nimodipine because it caused hypotension [14]. The historical question is no longer whether or not to reappraise nimodipine but rather how to use it consistently.

Source of support
No extramural funding supported this effort.

Conflict of interest
There are no conflicts of interest.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 4 December 2023 Accepted: 7 December 2023
Published online: 19 January 2024

References

1. Cohen R, Allen G. Cerebral arterial spasm: the role of calcium in in vitro and in vivo analysis of treatment with nifedipine and nimodipine, in Cerebral Arterial Spasm. Baltimore: Williams & Wilkins; 1980. p. 527–32.
2. Dreier JP, Windmüller O, Petzold G, et al. Ischemia triggered by red blood cell products in the subarachnoid space is inhibited by nimodipine administration or moderate volume expansion/hemodilution in rats. Neurosurgery. 2002;51(6):1457–65.
3. Allen GS, Bahr AL. Cerebral arterial spasm: part 10. Reversal of acute and chronic spasm in dogs with orally administered nifedipine. Neurosurgery. 1979;4(1):43–7.
4. Allen GS, Banghart SB. Cerebral arterial spasm: part 9. In vitro effects of nifedipine on serotonin-, phenylephrine-, and potassium-induced contractions of canine basilar and femoral arteries. Neurosurgery. 1979;4(1):37–42.
5. Auer LM. Pial arterial and venous reaction to intravenous infusion of nimodipine in cats. J Neurosurg Sci. 1982;26(3):213–8.
6. Peroutka SJ, Allen GS. Calcium channel antagonist binding sites labeled by 3H-nimodipine in human brain. J Neurosurg. 1983;59(6):933–7.
7. Auer LM, Ito Z, Suzuki A, Ohta H. Prevention of symptomatic vasospasm by topically applied nimodipine. Acta Neurochir (Wien). 1982;63(1–4):297–302.
8. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm–a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308(11):619–24.
9. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989;298(6674):636–42.
10. Wolf S, Martin H, Landscheidt JF, et al. Continuous selective intraarterial infusion of nimodipine for therapy of refractory cerebral vasospasm. Neurocrit Care. 2010;12(3):346–51.
11. Schwarting J, Harapan BN, Lin X, Plesnila N, Terpolilli NA. Nimodipine reduces microvasospasms after experimental subarachnoid hemorrhage. Stroke. 2023;54(10):2666–70.
12. DorhoutMees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007;2007(3):CD000277.
13. Rass V, Kindl P, Lindner A, et al. Blood pressure changes in association with nimodipine therapy in patients with spontaneous subarachnoid hemorrhage. Neurocrit Care. 2023;39(1):104–15.
14. Sandow N, Diesing D, Sarrafzadeh A, Vajkoczy P, Wolf S. Nimodipine dose reductions in the treatment of patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2016;25(1):29–39.