

Cerebral Vasospasm after Subarachnoid Hemorrhage and Tadalafil-Nimodipine Hypothesis

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Abstract

Cerebral vasospasm following subarachnoid hemorrhage (SAH) is a common reaction induced by multiple factors with unclear mechanisms. This complication is difficult to treat and puts patient at risk for developing a delayed ischemic neurological deficit that can lead to substantial morbidity and mortality. Although numerous strategies have been suggested for the treatment and prevention of cerebral vasospasm following SAH, no definitive effect has been concluded in this regard. In this paper, we hypothesize that phosphodiesterase-5 inhibitors, tadalafil, can be used together with nimodipine, a calcium channel blocker, to prevent vasospasm in patients with subarachnoid hemorrhage. With synergic effects, the proposed drugs can promote relaxation of smooth muscles in spastic vessels.

Keywords: Cerebral vasospasm; nimodipine; phosphodiesterase-5 inhibitor; subarachnoid hemorrhage; tadalafil

1. Introduction

Cerebral vasospasm is mainly observed in patients with subarachnoid hemorrhage (SAH) of a ruptured aneurysm and is widely accepted as a major cause of delayed cerebral ischemia (1). Indeed, cerebral vasospasm is the leading potentially treatable cause of death and disability in patients experiencing aneurysmal SAH (2). This phenomenon usually occurs between fourth and twelfth days after the initial SAH. Although pathogenesis of the cerebral vasospasm after aneurysmal SAH remains obscure, angiographic evidences often showed severe narrowing of intracranial

vessels. Some studies suggest that oxidation and/or free radical reaction after SAH may be involved in the occurrence of the cerebral vasospasm (3-5). Furthermore, a number of studies suggest that inflammatory reactions following SAH induced by cytokines and inflammatory cells may be attributed to the narrowing of the cerebral arteries (6,7). Therefore, inhibition of such processes may be an important therapeutic strategy for prevention of the vasospasm. Accordingly, pharmaceutical approaches, e.g. calcium antagonists and some peptides have been suggested (8). Several studies proposed that

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some vasodilator peptides including calcitonin gene-related peptide and vasoactive intestinal polypeptide may play an important role in the treatment of vasospasms (9,10). Some others revealed that phosphodiesterase inhibitors were effective in some cases, indicating the possibility of dysfunctional nitric oxide- cyclic 3',5'-guanosine monophosphate (cyclic GMP) pathway similar to that in ischemic stroke or cerebral vasospasm (11,12). In this paper we highlight the synergic effect of a long effect selective phosphodiesterase-5 inhibitor, tadalafil, and a calcium channel blocker, nimodipine, to prevent cerebral vasospasm in patients with SAH.

2. Hypothesis

We hypothesize that combined use of tadalafil and nimodipine can be applied to prevent and treat the cerebral vasospasm following SAH. These drugs have synergic effect on smooth muscle of the cerebral arteries.

3. Evaluation of the hypothesis

The cerebral vasospasm is an important and unexplained clinical problem in patients with SAH. In addition, the fatal problem caused by vasospasm is ischemic neurological deficit. The mechanism of cerebral vasospasm is complex and multi-factorial. Nitric oxide (NO) metabolism is one of the major possible pathogenesis. NO is a potent vasodilator and has an important role in progression of the cerebral vasospasm (13-15). NO increases the production of cyclic GMP, which induces relaxation of the smooth muscle. Cyclic GMP is gradually broken down by phosphodiesterase type 5 (PDE-5). This enzyme shows variations in tissue distribution, specialized functions in different vascular bed and is easily targeted by using selective inhibitors (16-18). PDE-5 is also present in the brain tissue and it has also been shown to be present and active in the guinea pig basilar artery (19-21). In the cerebral circulation, using selective phosphodiesterase inhibitors seems to be effective on treatment of

some conditions such as cerebral vasospasms after SAH and stroke (19). PDE-5 inhibitors potentiate the action of endogenous NO released from the endothelial cells lead to relaxation of smooth muscle of intracranial vessels (22). In rat a model, sildenafil, PDE-5 inhibitor, raised level of the cyclic GMP, angiogenesis and neurogenesis in the brain and also enhanced the functional recovery (23). However, in order to use more selective inhibitors and decreasing unexpected side effects, it is essential to know the exact distribution of the different phosphodiesterase families in cerebral arteries, and the role and importance of these molecules in the physiological reaction of the cerebral arteries (19). In a recent study by Koktekir and colleagues on rats, they first investigated the vasodilatory effects of tadalafil, a PDE-5 inhibitor, on the cerebral arteries with measurement of basilar artery diameters on angiography (24). They concluded that tadalafil had a vasodilatory effect on both acute and chronic periods of cerebral vasospasm following SAH [24]. On the other hand, nimodipine, a 1,4-dihydropyridine-derivative Ca^{2+} channel blocker, inhibits Ca^{2+} inflow via voltage-sensitive L-type Ca^{2+} channels and inhibits vascular smooth muscle spasm (15). Moreover, nimodipine has been found to have effects on cerebral vasospasm (25,26). A recent systematic review highlighted that among calcium antagonists, oral nimodipine was indicated in patients with aneurysmal SAH (27).

Taken together, the authors hypothesize that synergic effect of tadalafil, a selective PDE-5 inhibitor, and nimodipine, a calcium channel blocker, on cerebral vasospasm after SAH merits being investigated in experimental and human studies with regard to the treatment of delayed cerebral vasospasm and related ischemic neurological deficit.



Conflicts of interest

The authors declare that they have no conflict of interest.

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