MK 801: A Possible Neuroprotective Agent by Poststroke Depression?

To the Editor: Stroke is the third leading cause of death and adult morbidity in developed countries.[1] Many deleterious cellular pathways have been proposed to explain the molecular pathogenesis of this clinically devastating disease.[2] Interest in the role of neurotransmitters in the pathogenesis of ischemic stroke resulted in studies establishing that the release of glutamate and its excitotoxic actions through the *N*-methyl-D-aspartic acid (NMDA) receptors are significant in the development of ischemic neuronal damage.[2]

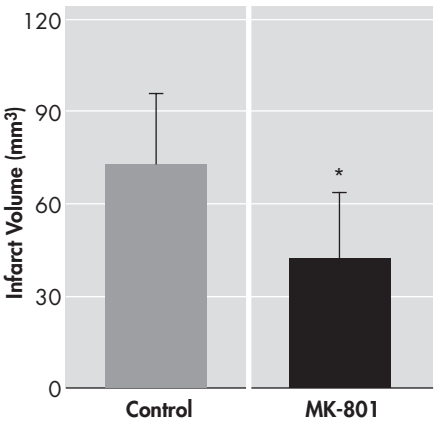
It is widely known that the occurrence of poststroke mood disorders, especially depression, is one of the most frequent complications of stroke.[3] It affects approximately 20% to 40% of all patients and the definitive treatment includes various antidepressant agents.[3] Interestingly, the evidence regarding antidepressant activity of NMDA receptor antagonists (especially MK 801) is rapidly replicating.[4,5] In light of these findings, we wanted to evaluate whether this novel antidepressant agent also has a neuroprotective effect by cerebral ischemia.

To examine this matter, we evaluated the neuroprotective effect of MK 801 (dizocilpine), a noncompetitive NMDA receptor antagonist, after transient focal cerebral ischemia, a relevant model for the thrombolyzed stroke in humans.

Anesthetized Wistar rats (330–370 g) were submitted to transient thread occlusion of the middle cerebral artery using an intraluminal filament technique.[6] The rectal temperature was maintained between 36.5°C and 37.0°C using a feedback-controlled heating system. The cerebral blood flow, measured by laser Doppler flowmetry, was reduced to ~15% of preischemic control levels immediately after thread insertion in all animal groups. MK 801 or vehicle was applied intraperitoneally (3 mg/kg) just after transient ischemia. Twenty-four hours after reperfusion, the area of infarction was measured by toluidine blue staining. This study was interesting with regard to poststroke depression by which a mood stabilizer with neuroprotective properties would be preferable.

MK 801 showed a significant neuroprotection ($p<0.05$, analysis of variance followed by least significant difference tests) after transient focal cerebral ischemia (73.12 ± 23.2 versus $23.12 + 21.1$) (Figure 1). In summary, this study indicates that even with a serious brain injury, MK 801 could exert a significant neuroprotective effect. However, further experiments to evaluate the long-term clinical reflections of such neuroprotective effects of MK 801 in poststroke depression patients via MRI and spectroscopy studies, would be logical future steps in the field of psychiatric research.

FIGURE 1. Infarct Volumes of Rats Subjected to Transient Cerebral Ischemia



Data are given as means ± SD
Animals treated with MK 801 (3 mg/kg) led to a decrease in infarct size.
*Significantly different from vehicle-treated control animals ($p \leq 0.05$).

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Management of Phantom Limb Pain and Sensation with Milnacipran

To the Editor: Phantom limb pain is classified as neuropathic pain that develops after nerve injury. It is an aftereffect of amputation occurring in up to 85% of patients who have undergone such surgery.[1] Tricyclic antidepressants have shown effectiveness in reducing phantom limb pain. Analgesic effects have been reported for venlafaxine, a novel serotonin (5-HT) and noradrenaline reuptake inhibitor (SNRI), against various types of neuropathic pain;[2] however, there are still no reports of a successful treatment for phantom limb pain. As far as we know, this is the first report of the successful management of phantom limb pain and sensation with milnacipran, which is another SNRI.

Case Report

A 77-year-old man with an above-knee amputation on his right leg for arteriosclerosis obliterans was transferred to the department of orthopedics for the purpose of right hip disarticulation due to osteomyelitis in the amputation stump. On the 11th day after the operation, he was referred to the department of psychiatry because he developed paroxysmal phantom limb pain "squeezed" in the absent right knee and ankle joint. Simultaneously, the patient experienced a phantom limb sensation as if the "amputated right lower extremity was actually present." He was not depressive, anxious, or hypochondriacal. He was administered 100 mg/day of fluvoxamine for 3 years after the first operation to treat depressive symptoms. Other therapy included 25 mg/day of quetiapine for delirium and 0.5 mg/day of etizolam for sleep disturbances after the last operation. Milnacipran, 30 mg/day, was added to the regimen. The abnormal pain and sensation were reduced after 1 week but did not vanish. The dosage of milnacipran was increased to 50 mg/day in order to reach remission. After 3 weeks of milnacipran therapy, the phantom limb pain and sensation completely disappeared without adverse events. He continued to take 50 mg/day of milnacipran and was discharged without relapse.

Discussion

In our case, milnacipran rather than fluvoxamine was likely successful in the management of phantom limb pain and sensation because these phenomena developed abruptly during the long-term administration of fluvoxamine and there was rapid dose-dependent improvement following administration of milnacipran. There is a significant amount of evidence to show that tricyclic antidepressants have analgesic efficacy against different kinds of pain due to their action on noradrenergic and serotonergic systems in descending inhibitory pain pathways.[3] Although several reports suggest that selective serotonin reuptake inhibitors (SSRIs) are also capable of alleviating neuropathic pain, meta-analysis found that tricyclic antidepressants showed outstanding analgesic efficacy as compared with SSRIs.[4] Therefore, reuptake inhibition of both 5-HT and noradrenaline arguably play an important role in analgesic efficacy. Milnacipran would reveal a prominent analgesic effect by selectively inhibiting the reuptake of both 5-HT and noradrenaline.[5] In addition, our patient experienced no adverse events. Milnacipran is devoid of affinity for various neuroreceptors associated with numerous adverse events.[5] From a clinical point of view, with respect to pharmacodynamic characteristics, milnacipran could be expected to have tolerability and a therapeutic effect for phantom limb pain and sensation.

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Alcoholic Optic Neuropathy: Another Complication of Alcohol Abuse

To the Editor: Alcohol affects both the central and the peripheral nervous system; hence, cognitive dysfunction as well as sensory and mo-