



Fampridine Therapy in Multiple Sclerosis: We Should Think Twice!

Multipl Sklerozda Fampiridin Tedavisi: İki Kere Düşünmemiz Gerekiyor!

© Mohamed SA Mohamed

Cologne University Faculty of Medicine, Department of General Medicine, Cologne, Germany

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Dear Editor,

Fampridine or 4-aminopyridine is a broad-spectrum blocker of the Kv1 family of voltage-gated potassium channels that is used as a symptomatic therapy for patients with certain neuromuscular disorders to enhance synaptic neuronal conduction (1). In multiple sclerosis (MS) [Expanded Disability Status Scale (EDSS) 4-7], it is used to improve walking ability and or ataxia. The drug blocks K⁺ channels involved in the establishment of early membrane hyperpolarization, thereby potentiating and prolonging membrane depolarization and the nerve impulse (2). However, the role of Fampridine in improving the manifestations of MS could be related to the following effects:

- Interference with the establishment of hyperpolarization in the neuronal cell membrane, allowing for prolonged cell membrane depolarization and accordingly stronger nerve impulse. This is helped by the physiologic subcellular localization of the Kv1 K⁺ channels at the presynaptic ends of neuronal cell membranes (3). However, this action is responsible for the main adverse effect of the drug that might develop in some patients, which is the development of seizures.

- Kv1.3 and Kv1.5 have been reported to play a significant role in immunomodulation and cellular activation, proliferation, and migration of lymphocytes (2). Accordingly, inhibition of these channels might contribute to the suppression of the demyelinating autoimmune pathogenesis of the disease.

- The demyelination associated with MS was found to be associated with the relocation of Kv1.1 and Kv1.2 from the typical juxta-paranodal sites to the nodes, together with a disproportionate

increase in the level of KV1.1 (4). Accordingly, inhibition of these channels through the Fampridine therapy could partially restore the physiologic monophasic compound action potential (4).

Thus, it seems that the drug is well suited to MS and similar disorders. However, there is another side of the drug that is not well investigated and should be carefully considered. The inhibition of Kv1.3 and Kv1.5, which are important for cellular proliferation and migration, is beneficial for immunomodulation when affecting lymphocytes. However, on the other side, it might impede regenerative abilities that are essential for disease control and or remyelination.

Moreover, although the various members of the Kv1 family have different signaling and little is known about their exact roles in disease and physiology, it is well established that these channels are involved in cell membrane hyperpolarization, and their blockade is associated with increased membrane depolarization and cellular excitability with the potential of the development of seizures, atrial fibrillation, and arterial myogenic vasoconstriction (5,6), which might potentiate ischemic events that may accidentally occur during the application of the therapy or even help their precipitation.

Spreading depression (SD) is a wave of membrane depolarization that occurs in the brain and is accompanied with vascular changes. The reason behind the development of SD is not fully clear, but it might result from differential ionic channels activities in various areas of the brain as a consequence of areal metabolic-perfusion mismatches (7). Under physiologic conditions, the duration of SD is too short to cause tissue injury. However, prolonged SD has

Address for Correspondence/Yazışma Adresi: Mohamed SA Mohamed MD, Cologne University Faculty of Medicine, Department of General Medicine, Cologne, Germany
Phone: +4915214736547 E-mail: mohammed.shehatta1@gmail.com ORCID ID: orcid.org/0000-0002-8922-5243

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been linked to the aura of migraine and ischemic stroke. Seizures, ischemia, and aura of migraine may share the common end result, which is increased membrane depolarization and accompanying hyper-excitability and or vasoconstriction (8,9).

Voltage-gated K⁺ channels (Kv channels) play an important role in the stabilization of the membrane potential and the establishment of hyperpolarization. Accordingly, inhibition of Kv channels is expected to potentiate and prolong SD. Based on these facts, Fampridine is used to initiate seizures in animals and its toxicity presented clinically in the form of ischemic stroke (5). This may reflect the important role of Kv channels in the clinical presentations of prolonged SD. Accordingly, openers of Kv channels are expected to protect against prolonged SD and its consequences (seizures, ischemia and or migraine with aura).

Clinically, this can be reflected in two aspects:

- First, it is very important to consider a strict risk-benefit assessment before starting Fampridine therapy. Patients with MS with 4-7 EDSS are usually older adults, who have the same community risk of stroke and epilepsy. They may even be under higher risk because of the decreased walking ability before therapy, which might be associated with obesity and hyperlipidemia, and a higher risk of falling and accompanied head injury. Although the normal control individual has a community risk of stroke, the degree of ischemia-reperfusion injury (IRI), and accordingly the neurologic deficits, might be reduced through the application of conditioning procedures such as ischemic and or pharmacologic conditioning. Potent pharmacologic conditioners include K⁺ channel activators. By giving Fampridine to improve a patient's walking ability, there might be an opposite conditioning towards a worse response toward coincidentally occurring ischemic events.

- Secondly, because the drug potentiates SD, which is linked to the aura of migraine, the drug should not be used in patients who suffer of migraine. On the other side, this can support the use of Kv channel openers such as retigabine as potential anti-migraine therapy.

Indeed, it is difficult to estimate whether the block of Kv1 K⁺ channels would be protective or harmful during IRI. From one aspect, hyperpolarization-inducing channels are expected to counteract the membrane depolarization that plays a major role in the pathogenesis of the injury. However, the inhibition of Na⁺/K⁺ ATPase during anoxia (ischemia) is responsible for increased intracellular Na⁺ and increased extracellular K⁺ around the cell membrane, which is the base of the associated membrane depolarization (10). Hence, a channel that allows a K⁺ outward flow might worsen the condition. Accordingly, further investigations in this regards are essential. However, the above-mentioned, well-established remarks might be enough to consider

a high degree of risk assessment and proper patient evaluation before the establishment of symptomatic or supportive therapy with Fampridine.

A proposed study for the experimental testing of the effect of Fampridine on coincidentally-occurring ischemic events: Using a suitable animal model, a double-blinded randomized study of two study groups could be conducted. A control group of animals subjected to no placebo or placebo treatment is to be compared with a study group of the same number, sex, age, and breeding conditions of animals subjected to therapeutic doses of Fampridine. All animals should be exposed to well-controlled ischemic events and the degree of clinical and pathologic effect should be evaluated and compared.

Ethics

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References

- Pickering H, Murray J, Lin CS, Cormack C, Martin A, Kiernan MC, Krishnan AV. Fampridine treatment and walking distance in multiple sclerosis: A randomised controlled trial. *Clin Neurophysiol* 2017;128:93-99.
- Comes N, Bielanska J, Vallejo-Gracia A, Serrano-Albarrás A, Marruecos L, Gómez D, Soler C, Condom E, Ramón Y Cajal S, Hernández-Losa J, Ferreres JC, Felipe A. The voltage-dependent K(+) channels Kv1.3 and Kv1.5 in human cancer. *Front Physiol* 2013;4:283.
- Trimmer JS. Subcellular localization of K⁺ channels in mammalian brain neurons: remarkable precision in the midst of extraordinary complexity. *Neuron* 2015;85:238-256.
- Bagchi B, Al-Sabi A, Kaza S, Scholz D, O'Leary VB, Dolly JO, Ovsepian SV. Disruption of myelin leads to ectopic expression of K(V)1.1 channels with abnormal conductivity of optic nerve axons in a cuprizone-induced model of demyelination. *PLoS One* 2014;9:e87736.
- Johnson NC, Morgan MW. An unusual case of 4-aminopyridine e toxicity. *J Emerg Med* 2006;30:175-177.
- Chen TT, Luykenaar KD, Walsh EJ, Walsh MP, Cole WC. Key role of Kv1 channels in vasoregulation. *Circ Res* 2006;99:53-60.
- Ayata C, Lauritzen M. Spreading Depression, Spreading Depolarizations, and the Cerebral Vasculature. *Physiol Rev* 2015;95:953-993.
- Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab* 2011;31:17-35.
- Chatterjee S, Nieman GE, Christie JD, Fisher AB. Shear stress-related mechanosignaling with lung ischemia: lessons from basic research can inform lung transplantation. *Am J Physiol Lung Cell Mol Physiol* 2014;307:668-680.
- Stys PK. Anoxic and ischemic injury of myelinated axons in CNS white matter: from mechanistic concepts to therapeutics. *J Cereb Blood Flow Metab* 1998;18:2-25.