4-Aminopyridine for symptomatic treatment of multiple sclerosis: a systematic review – 30199

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Multiple sclerosis (MS) is the most frequent nontraumatic cause of neurological deficit in young adults. It is a chronic inflammatory disease of the central nervous system characterized by demyelination which can cause axonal conduction block. The heterogeneous symptomatology includes paraesthesia, palsy, optic neuritis, diplopia, vertigo and bladder disturbances3,4-Diaminopyridine (DAP) and 4-aminopyridine (4-AP) are potent inhibitors of voltage gated potassium channels (Kv). In vitro studies have shown that DAP and 4-AP can improve conduction of action potentials in demyelinated nerve fibres and thereby increase the release of neurotransmitters in synapses and at the neuromuscular junction 4-AP is fat soluble and able to pass the blood–brain barrier Consequently, 4-AP has been applied in a number of treatment studies related to MS and is the focus of this review. Recently a sustained-release drug (SR-AP) was introduced into the market.

A number of reviews have addressed the effects of 4-AP and SR-AP in patients with MS, but so far few have paid attention to both experimental and clinical studies. In 2001 a Cochrane review on the topic was published which was updated in 2003. Mainly studies on 4-AP were included and only one study on SR-AP was identified. The conclusion of the Cochrane review was that no reliable statement concerning the safety and efficacy of 4-AP for treating symptoms in patients with MS could be made. In 2004 Hayes reviewed pharmacokinetic, experimental and clinical studies on 4-AP and one randomized, controlled trial on SR-AP, and concluded that SR-AP most likely yields fewer side effects and more robust clinical gains than 4-AP In 2007 the second trial on SR-AP was published. In January 2010, 4-AP extended release tablets for use at 10 mg twice daily were approved by the FDA for the improvement of walking in patients with MS and the overall conclusion of subsequent reviews; is that SR-AP notonly has a clinically meaningful beneficial effect on walking speed and muscle strength of the

lower extremities but also have effects in walking speed;dexetrity and long term effects on cognitive assessment parameters. 50% of patients MS will need help walking within 15 years after the onset of the disease.SR-AP have approved in four form MS.so use in patient wiht MS with EDSS 2.5 to 7. These latest reviews further conclude that SR-AP is generally well tolerated, most adverse events being mild to moderate. Moreover, only limited attention has been drawn to the potential effects on other bodily functions and symptoms than walking, as well as to explaining the clinical effects of the drug by means of the underlying mechanisms of action.

Keywords : Multiple sclerosis ,Clinical trials ,Walking speed, Dexetrity, Cognitive assessment, Safety .4-AP