METHOD OF TREATING OF DEMYELINATING DISEASES OR CONDITIONS

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BACKGROUND OF THE INVENTION

Multiple sclerosis (MS) is a degenerative and inflammatory neurological disease that affects the central nervous system, and is associated with formation of neuronal plaques and impaired neuronal conduction due to demyelination (loss of myelin). Similarly, extensive demyelination is commonly reported in spinal cord trauma and stroke (Bunge et al, 1993; Blight and DeCrescito, 1986; Pendlebury et al, 2000).

Basic research into the physiology of the action potential propagation in myelinated fibers showed that conduction block in demyelinated fibers was partly due to the appearance of aminopyridine-sensitive potassium channels in areas of myelin loss (Bever 1996).

Action potentials propagate along normal myelinated nerve fibers by a process of salutatory conduction, which results from a sodium current generated by the opening of voltage-sensitive sodium channels at the node of Ranvier. Thus, at the onset of electrical stimulation, sodium (Na^+) ions enter the neuron, causing the neuron to become more positively charged. When the positive nature of the neuron approaches a critical level, "depolarization" occurs. Depolarization allows a positive core of ions to flow down the neuron, along the axon and to the nerve ending. For the neuron to "reset" itself, the excess positive charge must be dissipated. This is done via the outflow of potassium ions (hereinafter "K^+") through potassium channels. When myelin is disrupted, voltage-sensitive potassium channels that open during depolarization appear on the axolemma. The potassium current, flowing opposite to the sodium current, decreases action potential amplitude and duration, contributing to conduction failure by decreasing the distal effective current densities. These conduction deficits are associated with disabling symptoms, including muscle weakness. By blocking the outflow of K^+ through potassium channels, the neuron remains depolarized longer and is more easily restimulated. Thus, potassium channel blockers are believed to be useful in the treatment of diseases and conditions which impair action potential transmission such as MS, Traumatic Brain Injury (hereinafter "TBI") and Spinal Cord Injury (hereinafter "SCI").

Potassium channel blockers, such as 4-amino pyridine (hereinafter "4-AP"), increase action potential duration and amplitude in demyelinated fibers and improve action potential propagation in vitro (Bostock et al, 1978; 1981; Targ and Kocsis, 1985; 1986; Shi and Blight, 1997), facilitate neurotransmitter release (Bostock et al, 1981; Hirsh and Quandt, 1993; Sherratt et al, 1980), and potentiate muscle contractility (Agoston et al, 1982; Savage et al, 1985). These observations suggested that potassium channel blockers, such as 4-AP, could restore conduction in demyelinated fibers in MS patients. Subsequent clinical trial results lend further support the proposition that aminopyridine treatment may improve symptoms in some MS patients (Jones et al 1983; Stefoski et al, 1987; Davis et al, 1990; van Diemen et al, 1992; Bever et al, 1994; Schwid et al, 1997).

4-AP has also been disclosed to be effective in the treatment of neurological conditions including SCI, reduction of chronic pain and spasticity in SCI patients, Alzheimer's disease, post-polio syndrome, myasthenia gravis, Huntington's disease, age-related memory disorders, post-traumatic, post-stroke or post-toxic syndromes affecting memory or cognition, and dysautonomia (Wurtman R J and Buyukuysal R, 1989; Hansebout R R and Blight A, 1996; Hansebout R R and Blight A 1994). Clinical studies for the use of Fampridine-SR in long-term spinal cord injured patients have begun (Potter et al, 1998a,b) notwithstanding safety concerns surrounding use of 4-AP in the general patient population (Multiple Sclerosis, Cognos Study #51, Decisions Resources, October, 1999; pp77–8). Several studies have shown that single doses of 4-AP can restore some function in SCI patients when administered one year or longer after injury (Potter et al, 1998a,b; Qiao et al, 1997; Hayes et al, 1993; 1994). Positive effects after chronic dosing have also been reported. Clinically significant functional improvements were observed in 16 out of 16 patients after 3 months of daily oral dosing with 30 mg/kg 4-AP in patients with SCI of 2 years or more. Some patients previously classified as having complete injury were reclassified to incomplete injury level (Segal et al, 1999). All patients showed some degree of improvement in at least some type of neurolgic or pulmonary function after 3 months of daily oral treatment with 4-AP (30 mg/day, or approximately 0.5 mg/kg). A lower dose was not active.

As previously stated, 4-AP blocks potassium channels, effectively prolonging the action potential. Unfortunately, this mechanism by which potassium channel blockers can improve symptoms associated with diseases and conditions which impair action potential transmission can also lead to epileptic-like activity. Indeed, 4-AP is a recognized convulsive agent in animals and humans. Therefore, the usefulness of 4-AP as a therapeutic agent for MS, TBI and SCI is tempered by its pro-convulsant liability and other undesirable side effects. Restlessness, confusion, and generalized tonic-conic seizures have been reported at doses higher than 0.8 mg/kg (Ball et al, 1979; Bever et al, 1994). Van Diemen et al (1993) reported that magnitude of improvement in MS patients (defined by improvement in smooth pursuit gain) was significantly related to 4-AP serum level, (33–75 ng/ml necessary for significant improvement after oral administration). However, side effects (paresthesia/dysestheia, dizziness/light-headedness, and even gait instability) were observed at the same doses. In another human study, Bever et al (1994) reported a grand mal seizure at a serum level of 104 ng/ml. Both groups of investigators suggested that higher dosages and serum levels would be likely to produce greater improvements in those MS patients which responded to lower doses of 4-AP. Thus, the degree of efficacy with 4-AP is dose- and side effect-limited.

Concern about the side-effects associated with higher 4-AP serum levels has led to the development of sustained release formulations (Fampridine-SR) (Masterson J G and Myers M, 1994; 1996a; 1996b). Fampridine-SR is currently in Phase 2 clinical studies for MS. Patients in prior clinical studies of Fampridine-SR have shown improvement in a variety of functions. Depending on the individual, these improvements have included enhanced bladder, bowel, and sexual function, increased ease of movement and sensation, and reduced muscle spasticity, fatigue and chronic pain.

Another approach to eliminating the undesirable side effects associated with 4-AP involves coadministration of 4-AP and voltage dependent sodium channel blockers. Sodium (Na^+) channel blockers block the inflow of Na^+ ions and reduce the susceptibility of the neuron to depolarization. This effectively reduces neuronal excitability. Indeed, it has been reported that coadministration of voltage-dependent