GV150526: A Neuroprotective Agent

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Key words: Excitotoxicity—Glutamate—GV150526—Glycine antagonist—MCAO—Neuroprotection—NMDA receptor—NMDA receptor antagonist—Stroke.

ABSTRACT

Thromboembolic stroke is a severe, disabling disease characterized by an abrupt reduction of cerebral blood flow, which leads to deprivation of oxygen and nutrients to neuronal tissue, followed by permanent brain damage. Evidence has been accumulated to implicate excitotoxicity in the pathogenesis of ischemic brain injury. Overstimulation of excitatory amino acid receptors becomes deleterious for neuronal cell survival. Glutamate antagonists can ameliorate the ischemic injury by any of several mechanisms. Because blockade of the glycine site of the N-methyl-D-aspartate (NMDA) receptor seems to offer a better side-effect profile, glycine antagonists are attractive targets for blocking excitotoxicity following stroke.

GV150526 is a selective and potent glycine antagonist at the NMDA receptor complex. It binds to the glycine site with both high affinity and high selectivity in in vitro binding studies. In vivo studies have shown that GV150526 significantly reduces infarct volume in the middle cerebral artery occlusion model of stroke. This effect remained statistically significant, even if treatment was delayed for as long as 6 h post-occlusion. GV150526 showed no evidence of adverse effects usually associated with NMDA receptor blockers, such as neuronal vacuolization in standard assays or cognitive impairment in behavioral tests. GV150526 had no significant treatment-related respiratory or cardiovascular effects or effects on behavior, body temperature, or blood pressure in mice or rats. Pharmacokinetic studies indicated that GV150526 has low clearance and volume of distribution in both the rat and the dog. Preclinical toxicology studies have shown that the compound is well tolerated in both species. Phase I/II studies were undertaken to assess the safety, tolerability, and pharmacokinetics of GV150526 in healthy volunteers and acute stroke patients, and from these a dose was selected to be studied in Phase III clinical trials. These efficacy studies have now completed recruitment and data reconciliation is ongoing. GV150526 has the potential to be an effective therapy for acute ischemic stroke.