

BMS-204352: A Potassium Channel Opener Developed for the Treatment of Stroke

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Key words: BK channel—Ca²⁺-Activated K⁺ channel—Cerebral ischemia—hSlo channel—Maxi-K channel—Neuronal hyperexcitability.

ABSTRACT

During ischemic stroke, a fatal biochemical cascade that results in neuronal hyperexcitability is initiated when neurons at risk are exposed to excessive excitatory amino acids and pathologically high levels of intracellular calcium (Ca²⁺). Therefore, neuroprotectants including NMDA-antagonists and blockers of voltage-gated Ca²⁺ channels have been proposed as novel strategies for stroke treatment. Since potassium channels are key players in the control of neuronal excitability, and activation of neuronal potassium channels decrease excitability and neurotransmitter release, a novel approach for targeting acute ischemic stroke has been to develop openers of neuronal potassium channels. Bristol-Myers Squibb is developing BMS-204352, a fluoro-oxindole potassium channel opener, as a potential neuroprotectant for the treatment of acute ischemic stroke. BMS-203252 is a potent and effective opener of two important subtypes of neuronal potassium channels, the calcium-activated, big-conductance potassium channels (K_{Ca} channels) and voltage-dependent, non-inactivating potassium channels known as KCNQ channels. BMS-204352 (0.3 mg/kg, i.v.) significantly reduced cortical infarct volume in a model of permanent occlusion of the middle cerebral artery (MCA) in spontaneous hypertensive rats (SHR), as compared to vehicle when administered 2 h post-occlusion. At doses from 1 µg/kg to 1 mg/kg i.v., BMS-204352 produced a significant reduction in cortical infarct volume in normotensive Wistar rats. In healthy humans, single and multiple i.v. doses of BMS-204352 (0.001 to 0.2 mg/kg) were safe, well-tolerated and without psychomotor function effects. Multiple doses of BMS-204352 (0.1–2 mg/kg i.v.) administered within 48 h after stroke onset were well tolerated in patients in Phase II studies, designed to evaluate safety, tolerability and pharmacokinetics. No clinically significant differences in organ toxicity or adverse effects were found, and total clearance and volume of distribution were independent of dose. BMS-204352 failed to show superior efficacy in acute stroke patients compared to placebo in a Phase III study that included 1978 patients at 200 centers worldwide.