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Research and Development of Rho Kinase Inhibitor Eril

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Cerebral vasospasm is still the leading cause of poor postoperative outcome in patients with aneurismal subarachnoid hemorrhage. The Rho kinase inhibitor Eril – the first drug to be developed by specifically targeting a protein-kinase - was approved in Japan for the treatment of cerebral vasospasm after surgery for subarachnoid haemorrhage, and associated cerebral ischaemic symptoms. Rho-kinase is an important downstream effector of Rho GTPase. Activation of Rho kinase catalyzes phosphorylation of the myosin-binding subunit (MBS) of myosin light-chain phosphatase (MLCP), resulting in inhibition of MLCP and increased MLC phosphorylation. The phosphorylation of MLC allows MLC to interact with actin filaments. This interaction supports cellular processes dependent upon the generation of force by the cytoskeleton, such as control of cell shape, polarity, motility, and adhesion. Consequently, Rho kinase may regulate various pathological processes during vascular diseases including cerebral vasospasm. In in vitro studies, fasudil significantly inhibited not only vasocontraction but also neutrophil motility. The intravenous infusion of Eril prevented the occurrence of chronic cerebral vasospasm in a two-hemorrhage canine vasospasm model. Eril inhibited endothelial damage and neutrophil infiltration in the same canine model. A prospective randomized placebo-controlled double-blind trial of Eril was undertaken to determine the drug's effect on delayed cerebral vasospasm in patients with a ruptured cerebral aneurysm. Eril significantly reduced angiographically demonstrable vasospasm, symptomatic vasospasm, the occurrence of low-density on CT and the number of patients with a poor clinical outcome. Accumulating evidence suggests that Rho kinase is substantially involved in the pathogenesis of a wide spectrum of vascular diseases and that Rho kinase inhibitors such as Eril are useful for the treatment. Since its launch, clinical use of Eril has been very high and widespread in patients with subarachnoid hemorrhage. Eril successfully pioneered the present expanded discovery and development of various kinase inhibitors.