Beneficial Effect of the Combination of Idebenone and Manidipine 2HCl on Neurological Deficits and Histological Changes Following Cerebrovascular Lesions in Stroke-prone Spontaneously Hypertensive Rats. Yasutaka Nagisa, Tomoko Mihara, Kazuhiro Hamajo, Tetsuji Imamoto and Akinobu Nagaoka. Pharmaceutical Research Laboratories I, Takeda Chemical Industries, Ltd., Osaka 532

We investigated the effects of the combination of idebenone, an energy metabolism enhancer, and manidipine 2HCl, a dihydropyridine-derivative calcium antagonist, on neurological deficits and histological changes in the brain and the kidneys in stroke-prone spontaneously hypertensive rats (SHRSP) with cerebrovascular lesions (stroke).

SHRSP were kept on 1% NaCl solution as drinking water to synchronize the onset of stroke. After the onset of stroke symptoms, the salt solution was replaced with tap water. On the day following the onset of stroke, idebenone (50mg/kg), manidipine 2HCl (2mg/kg), or a combination of idebenone (50mg/kg) and manidipine 2HCl (2mg/kg) was administered orally once a day for 3 weeks.

1. In vehicle-treated control SHRSP with stroke, the body weight did not increase. Manidipine 2HCl increased the body weight, significantly. In the combination group, the body weight increased significantly after the 6th day of administration as compared to the control group and the idebenone-treated group.
2. Manidipine 2HCl ameliorated the neurological deficits after the onset of stroke during the entire experimental periods, and shorten the days with severe neurological deficits. The combination of manidipine 2HCl and idebenone significantly ameliorated the neurological deficits during the entire experimental periods as compared to the control group and the idebenone-treated group, and significantly shorten the days with severe neurological deficits as compared to the control group.
3. After the onset of stroke, the incidence of recurrence, which was frequently observed in the control group, was reduced in the manidipine 2HCl-treated group and the combination group.
4. Three weeks after the onset of stroke, hemorrhage, vascular necrosis, spongy degeneration, malacia and cavitation in the brain and tubular atrophy and proliferative and necrotic changes in the afferent arterioles in the kidneys were observed in the control group. In manidipine 2HCl-treated group and the combination group, these pathohistological changes in the brain were decreased. In the combination group tubular basophilic changes in the kidneys were ameliorated as compared to the idebenone-treated group.

In conclusion, the combination of idebenone and manidipine 2HCl ameliorated the change in body weight and the neurological deficits in SHRSP with stroke as compared to individual administration of each agent. We concluded that manidipine 2HCl enhances the therapeutic effect of idebenone in the treatment of cerebrovascular diseases.