7) Prophylactic and therapeutic effects of a novel Ca antagonist (S-312) in SHRSP. Masao Masui, Masaru Kawakami, Mikinori Torii, Hiroyuki Ito* and Motohiko Ueda. Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka 553 and * Kinki University School of Medicine, Osaka 589

It was reported that intraduodenal administration of S-312 (Methyl-4,7-dihydro-3-isobutyl-6-methyl-4-(3-nitrophenyl) thieno[2,3-b]pyridine-5-carboxylate) caused significant increases of vertebral blood flow in dogs1) and regional cerebral blood flow in SHRSP2). Daily oral administration of 1% gum arabic suspension of S-312 lowered the incidence of stroke in SHRSP. These effects seemed to be mainly related to its acute antihypertensive effects3). In this study, prophylactic and therapeutic effects of S-312 for occurrence of stroke were investigated using SHRSP.

Methods 1) Prophylactic effect: Polyethylene glycol (PEG) solution of S-312, nifedipine (Nif), or nicardipine (Nic) was orally administered once a day to male SHRSP at 9 weeks of age for 60 days. 2) Therapeutic effect: PEG solution of S-312, Nif, Nic, nimodipine (Nim), or flunarizine (Flu) was orally administered once a day to male SHRSP showing some symptoms of stroke for 4 weeks.

Results 1) Prophylactic effect: Life span of SHRSP was extended by administration of Ca antagonists in the following order; S-312 > Nif > Nic. Same order of potency was observed for the acute antihypertensive effect in SHRSP. Incidence of stroke (softening and/or hemorrhage) was the lowest in the SHRSP administered S-312. 2) Therapeutic effect: With dose above 3 mg/kg of S-312, some symptoms related with stroke were improved and marked increase of body weight was observed, while improvement of such symptoms with Nif, Nim, and Flu were transient. Increase of body weight was observed in 10 mg/kg of Nic and Nim, or 30 mg/kg of Flu. Life span of SHRSP was extended by administration of S-312 at 3 mg/kg. Following order of potency was observed; S-312 > Nic > Nim = Nif > Flu. Histological examination of brain of SHRSP showed that appearance of scar was increased by administration of S-312 at 10 mg/kg.

Therapeutic effects of S-312 for SHRSP would be explained by following mechanisms; 1) prevention of further deterioroliation of stroke by the antihypertensive effect due to it's Ca antagonism, 2) limitation of infarct size by well keeping of cerebral blood flow to neighbouring region.

2) M. Ninomiya et al., 74th Kinki Regional Meeting of Japan Pharmacological Association (Nov. 18, 1988)  