29) Effect of AJ-3941, a novel calcium antagonist on the development of stroke in SHRSP. Hisao Minato, Hiroshi Kato, Kayoko Zushi and Yoshinobu Masuda. Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Suita/Osaka 564, Japan.

INTRODUCTION

It has been reported that SHRSP develops the stroke with hypertension. These symptoms in SHRSP are known to accelerate by a excessive NaCl loading. In the present study, we investigated the effect of AJ-3941, [11-(4-cinnamyl-1-piperazyl)-3-fluoro-6,11-dihydrodibenzo[b,e]oxepine dimaleate], a structurally new class of calcium antagonist with cerebrovascular selectivity on the development of stroke in SHRSP.

MATERIALS AND METHODS

1) Normal diet group: Male SHRSP at 12 weeks old were fed with a standard diet (SP chow, Funabashi, Chiba, Japan) and water ad libitum. AJ-3941 and flunarizine were given a oral dose of 10 mg/kg once a day for 18 - 20 weeks. During the study, the neurological signs of stroke and the incidence of death were observed. Blood pressure and urinary protein excretion were measured at several points during the experiment.

2) 8% NaCl diet group: Male SHRSP at 12 weeks old were fed with a SP chow containing 8% NaCl and water ad libitum. AJ-3941 and flunarizine were orally given once a day for 6 weeks at a dose of 10 mg/kg and 30 mg/kg, respectively. During the study, the neurological signs of stroke and the incidence of death were observed. Blood pressure and urinary protein excretion were measured every week. In the series of two experiments, pathological findings including brain and kidneys in all animals used were determined.

RESULTS

1) Normal diet group: The blood pressure in the vehicle control group reached to around 230 mmHg at age of 20 weeks and this level of blood pressure maintained through the experiment. The mortality in vehicle control increased gradually with age advanced and almost a half of animals died caused by apoplexy during the experiment. AJ-3941 did not produce any lowering effects on blood pressure during the experiment. On the other hand, flunarizine exerted a significant reduction of blood pressure from 4 weeks of administration. AJ-3941 almost completely prevented the incidence of mortality. Furthermore, AJ-3941 markedly suppressed the brain edema, hemorrhage and nephrosclerosis in pathological observation. On the other hand, flunarizine did not show any preventive effects on the incidence of mortality.

2) 8% NaCl diet group: The characteristics in SHRSP were accelerated by NaCl loading. The salt loading to SHRSP markedly enhanced the neurological signs of stroke and shortened their survival periods. AJ-3941 (10 mg/kg) and flunarizine (30 mg/kg) significantly prevented the development of stroke signs and prolonged their life-span as well as the inhibition of proteinuria. In the pathological observation, both drugs significantly reduced the occurrence of brain edema and hemorrhage.

DISCUSSION AND CONCLUSION

The effect of a new class of calcium antagonist, AJ-3941 was investigated on the development of stroke in SHRSP which were fed with two different diets. AJ-3941 at a dose of 10 mg/kg clearly prevented the development of stroke in both of normal and high salt diet groups of SHRSP. On the other hand, flunarizine at the dose of 10 mg/kg did not show any preventive effects in normal diet group despite of lowering blood pressure, but showed a significant prevention in the development of stroke in salt diet group at a dose of 30 mg/kg which was three times as much as AJ-3941. From the present results, it was suggested that AJ-3941 was more beneficial than flunarizine in the prevention of stroke in SHRSP. The preventive effect of AJ-3941 may be brought about through its combined properties of the selective cerebrovascular action and the cerebral protection against the damage from cerebral ischemia.