Effect of chronic YM-358, a nonpeptide AT₁ receptor antagonist, on diurnal rhythm of blood pressure, heart rate and locomotor activity in stroke-prone spontaneously hypertensive rats. Norikazu Yamaguchi, Kazuko Fujimoto, Takeshi Suzuki, Takeshi Fujii, and Koichiro Kawashima. Department of Pharmacology, Kyoritsu College of Pharmacy, Tokyo 105

INTRODUCTION

YM-358 (2,7-diethyl-5-[2',(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-5H-pyrazolo[1,5-b][1,2,4]triazole potassium salt) is a structurally new nonpeptide AT₁ receptor antagonist. A single oral administration of YM-358 produced a dose-related reduction of blood pressure in renal hypertensive and spontaneously hypertensive rats (SHR). In the present study, we investigated the effect of daily administration of YM-358 for 4 weeks on the diurnal variation in mean arterial pressure (MAP), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate and locomotor activity using radio-telemetry in stroke-prone SHR (SHRSP). In addition, the measurements were continued for 7 days after stopping YM-358 to determine whether there was a rebound increase in blood pressure.

MATERIALS AND METHOD

At 22 weeks of age, the rats were anesthetized with 50 mg/kg pentobarbital sodium i.p. and the tip of catheter which refers pressure to sensor consisting of an implantable transmitter was inserted, and secured in the abdominal aorta about 5 mm below the renal artery. Two weeks after surgery, the rats were administered 10 or 30 mg/kg of YM-358 orally, or distilled water (2 ml/kg) once daily for 4 weeks at 19:00h. The rats were also observed for 7 days after stopping drug therapy.

RESULTS AND DISCUSSION

A clear diurnal variation in MAP, heart rate and locomotor activity was observed in synchrony with the light cycle before the start of therapy. MAP was slightly higher during the dark phase than during the light phase. Heart rate and locomotor activity were markedly higher during the dark phase than during the light phase, and decreased sharply soon after the lights went off. YM-358 at a dose of 30 mg/kg, p.o. per day produced a significant and consistent reduction in 24-hr MAP preventing the development of hypertension. YM-358 reduced DAP more than SAP suggesting that it may affect mainly vascular tone. YM-358 did not affect diurnal rhythms in heart rate and locomotor activity. The MAP determined 23h after the administration of YM-358 30 mg/kg showed a slight reduction. There was no rebound increase in blood pressure after the termination of therapy with YM-358. The results suggest that repeated oral administration of YM-358 for 4 weeks produce a consistent antihypertensive effect without affecting the heart rate, locomotor activity and diurnal variation in adult SHRSP rats. It is concluded that YM-358 has utility for treatment of hypertension.