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〔原　　著〕

Interaction between Hydralazine Derivatives and Propranolol on Blood Pressure in Conscious Rats*1

Kazunobu Sugawara
(Department of Pharmacy, Yamagata University Hospital*2)
Keiki Tanno
(Depatment of Pharmacy, Niigata University Hospital*3)
Masayori Ozaki
(2nd Department of Pharmacology, Nagasaki University School of Medicine*4)

Summary

The cardiovascular effects in combination with hydralazine or ecarazine and propranolol were investigated in conscious normotensive rats. Hydralazine (0.5, 1 and 2 mg/kg, i.p.) or ecarazine (2.5, 5 and 10 mg/kg, i.p.) alone produced a hypotensive action and tachycardia. Also propranolol (1 and 5 mg/kg, i.p.) alone produced a hypotensive action. A combination with hydralazine or ecarazine and propranolol showed slightly more effective hypotension than hydralazine or ecarazine alone without producing tachycardia. However, these hypotensive effects were diminished by administration of higher doses each other. The optimal dose which indicated the hypotensive action without producing tachycardia was the combination with hydralazine 1 mg/kg or ecarazine 5 mg/kg and propranolol 1 mg/kg. These results suggest that the choice of optimal doses may be necessary when propranolol is used in combination with hydralazine or ecarazine.

Introduction

Hydralazine is a potent hypotensive agent which the hypotensive mechanism depends on a decrease in peripheral vascular resistance[1]. The pronounced tachycardia, one of well-recognized side effects induced by hydralazine, loads the heart heavily for the treatment of hypertension.

On the other hand, β-adrenoceptor blocking agents have been introduced as therapy for hypertension in addition to that for cardiac arrhythmias and angina pectoris. Since β-ad-

*1 This work was reported at the 10th Meeting of Research on Drug Interaction, Aomori, May 1980.
*2 Nishinomae, Zao Iida, Yamagata 990-23, Japan.
*3 1-754 Asahimachitori, Niigata 951, Japan.
*4 12-4 Sakamotomachi, Nagasaki 852, Japan.

renoceptor blocking agents which do not have an intrinsic sympathomimetic activity decrease the heart rate, these agents are used clinically in combination with hydralazine[2),3)].

We investigated the effects of several β-adrenoceptor blocking agents including propranolol on the blood pressure in conscious rats by giving different doses via various routes of administration, and found that an acute hypotensive effect was exerted when optimal doses of these agents was given i.p.[4),5)].

In the present paper, therefore, the combined effects of hydralazine derivatives and β-adrenoceptor blocking agents on the blood pressure were studied experimentally in conscious normotensive rats. Hydralazine, ecarazine which was prepared for the reduction of side effect of hydralazine and propranolol were used in this study.

Materials and Methods

1. Animals

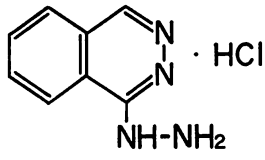
Male Kyoto Wistar strain rats (WKY) weighing 300-400 g were bred in our own laboratory.

2. Measurement of Blood Pressure and Heart Rate

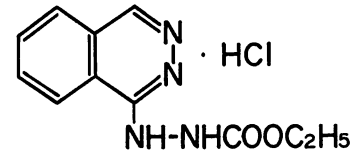
With the rats in a conscious but slightly restrained state, the systolic blood pressure (SBP) was measured using an electrosphygmomanometer (Narco Biosystem Co.) at 30 min, 1, 2, 3, 4, 5, 6 and 24 hr after a single i.p. administration of a given dose of test compounds or after administrating two drugs at the same time. Rats were warmed for 10-15 min ($38\pm2^{\circ}C$) before the measurements. Four pressure measurements were recorded in each animal and the mean was taken as the SBP. The heart rate (HR) was measured by HR monitor.

3. Drugs

The following drugs were used: hydralazine hydrochloride (Ciba), ecarazine hydrochloride (todralazine hydrochloride, Kyowa Hakko) and propranolol hydrochloride (ICI). All drugs were dissolved in 0.9% saline and the doses given refer to the salt.



Hydralazine HCl



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4. Statistical Methods

Values are expressed as the means±S.E. The statistical significance of differences between mean values was analyzed by Student's t test.

Results

1. Effect of Hydralazine or Ecarazine Alone

The basal SBP of the conscious rat was 128±2 mmHg (n=29) and HR was 341±6 beats/min (n=29). SBP and HR were not altered by i.p. administered saline.

Hydralazine produced an acute hypotensive action (10-30 mmHg) and an increase of the heart rate (50-100 beats/min) with the maximal response at 2 hr in doses of 0.5, 1 and 2 mg/kg and these actions were dose-dependent (Fig. 1). These hypotension and tachycardia recovered to the initial level 24 hr after administration.

Although the SBP and HR were not altered by a dose of 1 mg/kg, dose-dependent hypotensive action and tachycardia were produced by doses of 2.5, 5 and 10 mg/kg of ecarazine as well as the response with hydralazine (Fig. 2). However, the hypotensive action of ecarazine was more lasting than that of hydralazine.

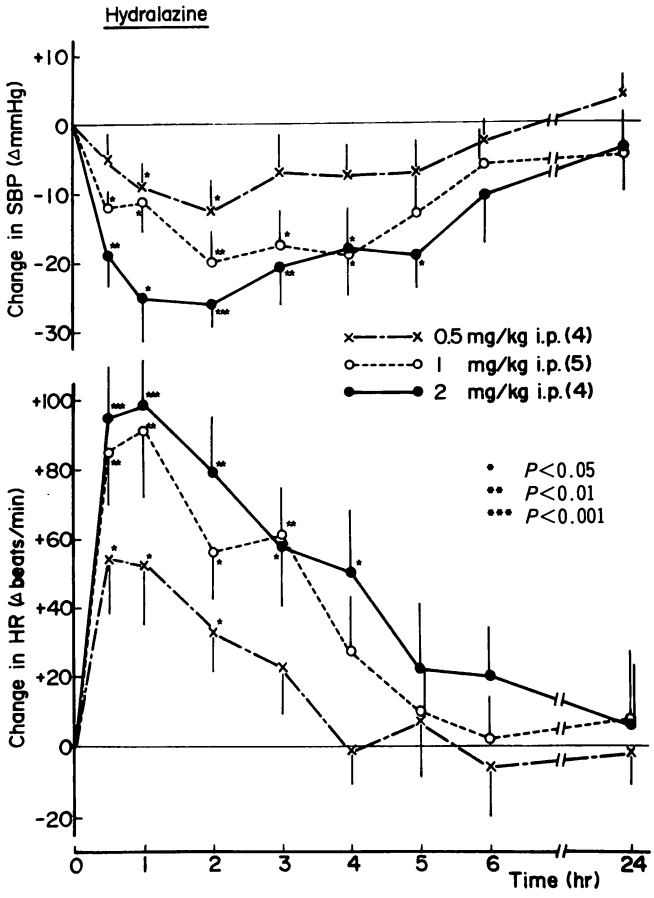

Fig. 1. Effect of hydralazine on systolic blood pressure (SBP) and heart rate (HR) in conscious normtensive rats. Number of rats used is indicated in parentheses. Vertical bars represent standard error of the mean. Significant difference from control (saline): $*P<0.05$, $**P<0.01$, $***P<0.001$.

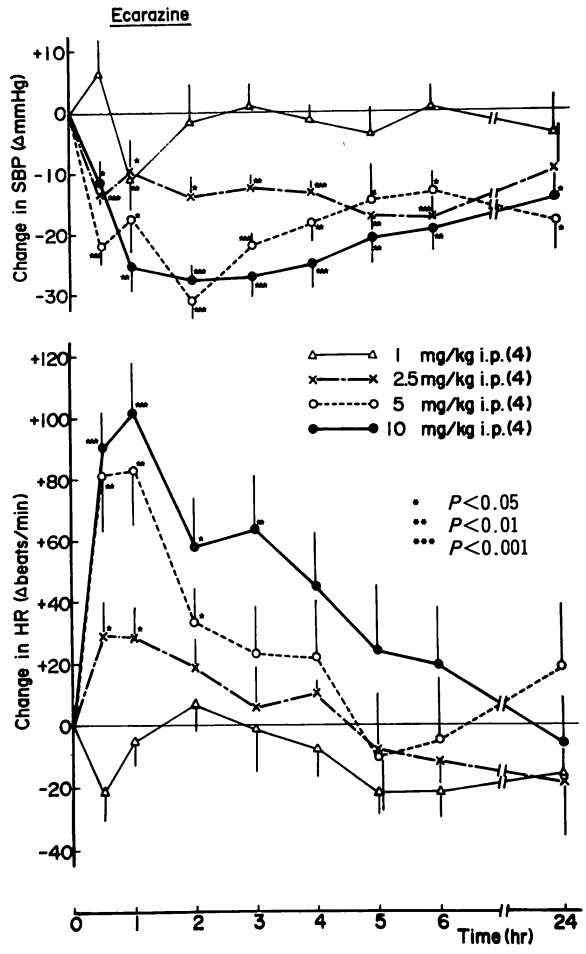

Fig. 2. Effect of ecarazine on SBP and HR in conscious normotensive rats. For details see Fig. 1.

2. Combination Effect with Hydralazine or Ecarazine and Propranolol

Protocol of combination with hydralazine or ecarazine and propranolol was as follows : (1) hydralazine 0.5 mg/kg+propranolol 1or 5 mg/kg, (2) hydralazine 1 mg/kg+propranolol 1 or 5 mg/kg, (3) ecarazine 2.5 mg/kg+propranolol 1 or 5 mg/kg, (4) ecarazine 5 mg/kg+propranolol 1 or 5 mg/kg.

The increase of HR induced with hydralazine (0.5 and 1 mg/kg) alone was markedly suppressed by combination with 1 or 5 mg/kg of propranolol, but the hypotensive effect did not reflect necessarily as an additive effect. A combination with hydralazine 1 mg/kg and propranolol 1 mg/kg showed slightly more effective hypotension than hydralazine alone. However, the hypotensive action induced by hydralazine 1 mg/kg and propranolol 5 mg/kg was less effective than that induced by propranolol alone (Fig. 3). A combination of the optimal dose which indicated the hypotensive action without producing tachycardia was the combination with hydralazine 1 mg/kg and propranolol 1 mg/kg.

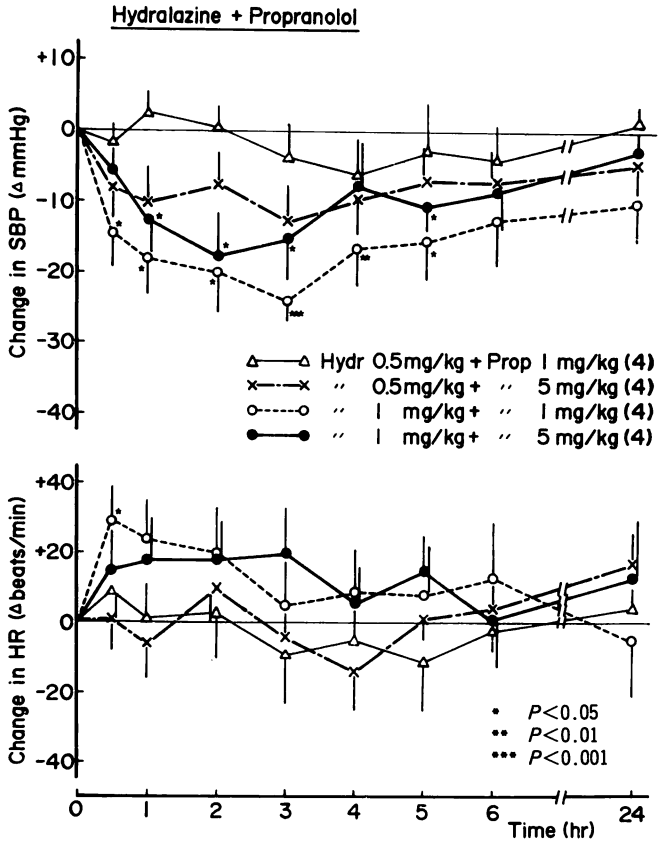

Fig. 3. Combination effect with hydralazine (Hydr) and propranolol (Prop) on SBP and HR in conscious normotensive rats. For details see Fig. 1.

In the case of interaction between ecarazine (2.5 and 5 mg/kg) and propranolol (1 and 5 mg/kg), on the other hand, a combination of the optimal dose which abolished the tachycardia induced by ecarazine and produced effective hypotensive action was the combination with ecarazine 5 mg/kg and propranolol 1 or 5 mg/kg (Fig 4).

Discussion

Several antihypertensive agents have been used for the treatment of essential hypertension. In recent years, there are a number views what is the first of drung in this hypertension. In 1978, Expert Committee in WHO proposed "Stepped-Care Therapeutic Programmes" for the therapy of hypertension, introducing a double system of diuretics and β-adrenoceptor blocking agents as the first choice drugs[6]. Although β-adrenoceptor blocking agents have been using instead of the thiazide diuretics as the first choice drugs in Europe and America, they not in our country since there is a difference between the diets.

Diuretics or β-adrenoceptor blocking agents have been used in combination with other antihypertensive agents for the treatment from light hypertension to moderate hypertension. Also the combination therapy with thiazides, β-adrenoceptor blocking agents and vasodila-

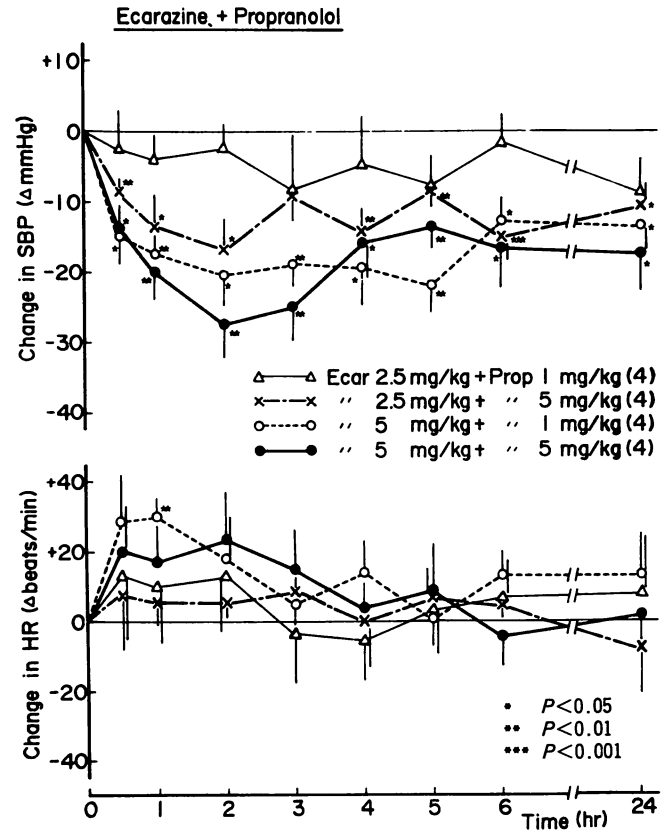

Fig. 4. Combination effect with ecarazine (Ecar) and propranolol (Prop) on SBP and HR in conscious normotensive rats. For details see Fig. 1.

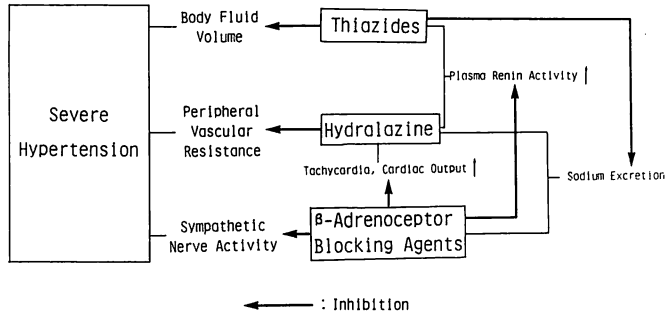

Fig. 5. Combination therapy with thiazides, hydralazine and β-adrenceptor blocking agents for severe hypertension.

tors is common in the treatment of severe hypertension (Fig. 5)[7]. Particularly this therapy has an advantage which each drug reduces mutually untoward effects and this may be an important aspect of the combined antihypertensive regime[8].

In the present study, the combined effects with hydralazine or ecarazine and propranolol were investigated without combining with thiazides since it was difficult to demonstrate the

acute hypotensive effect of thiazides in rats. Hydralazine or ecarazine alone produced a hypotensive action and tachycardia, and the combination with an optimal dose of propranolol abolished only tachcardia without altering the hypotensive effect. However, these hypotensive effects were diminished by administration of higher dose each other, remained as tachycardia was suppressed.

Sugawara *et al.*[4),5)] reported that an acute hypotensive effect was exerted when optimal dose of propranolol was given i.p. but these hypotensive effects were diminished by administration of higher doses in conscious normotensive rats, and that the masking action of the hypotensive effect may be attributed to the liberation of catecholamines from the adrenal medulla[9),10)].

Also, McLean *et al.*[11)] investigated interaction in combination with hydralazine and propranolol in healthy normotensive subjects, and reported that hydralazine induced significantly variable increases in the peak concentrations of propranolol and in the area under the propranolol concentrations without changing the recovery of metabolites in urine or in the systemic clearance of propranolol. They suggested that the concentration of propranolol in plasma was increased since hydralazine enhanced the systemic availability by lowering of first-pass hepatic clearance of propranolol absorbed from the digestive tract.

On the other hand, there was a clinical report in which the patient had a paradoxical rise of blood pressure after taking hydralazine while using propranolol and bendrofluazide[12)].

From these results, it could be considered that the diminishing hypotensive effects induced in combination with hydralazine and propranolol may depend on the increased plasma concentration of propranolol by hydralazine.

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