
ANTIHYPERTENSIVE ACTIVITY OF BUCUMOLOL, A β-ADRENERGIC BLOCKING AGENT, IN SPONTANEOUSLY HYPERTENSIVE RATS

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Effects of bucumolol, a β-adrenergic blocking agent, on blood pressure and the renin angiotensin system were studied in spontaneously hypertensive rats (SHR). The results were compared with those of propranolol at an equipotent dose in β-adrenergic blocking activity. Bucomolol lowered blood pressure and decreased plasma renin concentration (PRC) in both acute and long-term experiments. There was a significant correlation between percent changes in blood pressure and PRC following a single administration of bucumolol. Decrease in PRC persisted for the 6-week observation period despite the sustained reduction in blood pressure. On the other hand, propranolol did not lower blood pressure in acute experiment while it decreased renin release. These results suggest that inhibition of renin release is involved in the antihypertensive action of bucumolol.

Keywords—bucumolol; β-blocker; SHR; renin-angiotensin system; antihypertensive action; plasma renin concentration; plasma aldosterone concentration

INTRODUCTION

Inhibition of renin release has been considered to be one of the major factors involved in the antihypertensive action of β-adrenoceptor blocking agents. However, the relationship between changes in blood pressure and plasma renin activity (PRA) is not simple; propranolol does not lower blood pressure in spontaneously hypertensive rat (SHR) while it reduces PRA and pindolol lowers blood pressure without affecting PRA. Their complicated pharmacological actions other than β-adrenergic blocking action accounts for this situation.

Bucumolol is a new β-adrenergic blocking agent which is devoid of sympathomimetic action and does not cross the blood brain barrier. The agent has been shown to be more potent than propranolol in β-adrenergic blocking activity and far less potent in membrane stabilizing as well as local anesthetic actions. However, its antihypertensive activity has not been evaluated. Since bucumolol produces relatively pure β-adrenergic blockade, its antihypertensive action, if any, may be closely related to the inhibition of renin release.

The purpose of the present study was to determine if bucumolol lowers blood pressure in SHR and to examine the relationship between changes in blood pressure and plasma renin concentration (PRC). We studied the effects of single and long-term administrations of bucumolol on blood pressure and the renin-angiotensin system. The effects were compared between bucumolol and propranolol at equipotent doses in β-adrenergic blocking action.

METHOD

Male SHR of 15 and 5 weeks of age were used for acute and long-term experiments respectively. Both acute and long-term experiments consisted of 3 groups: control, bucumolol and propranolol groups which received oral administration of water 2 ml/kg, bucumolol 50 mg/kg and

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propranolol 100 mg/kg respectively. Bucumolol hydrochloride and propranolol hydrochloride were dissolved in water at a concentration of 25 mg/ml and 50 mg/ml respectively, and were administered by gavage in a volume of 2 ml/kg.

In acute experiments, a cannula was placed in the abdominal aorta via the femoral artery under pentobarbital anesthesia and the other end of the cannula was exteriorized at the neck. Two days later, mean blood pressure (MBP) and heart rate were measured by means of a polygraph (Nihon Kohden RM-150) before and 3 hours after oral administration of the β-adrenergic blocking agents. In long-term experiments, blood pressure and heart rate were measured once a week by the tail plethysmography (Narco, PE-300) 3 hours after dosing. At the 6th week of dosing the animals were cannulated in the abdominal aorta for blood sampling.

To determine PRC and plasma aldosterone concentration (PAC), blood samples were carefully withdrawn from the aortic cannula right before measurement of blood pressure. Immediately after sampling, the same amount of saline was infused. Blood samples collected in cooled microtubes containing EDTA were centrifuged at 3000×g for 20 minutes to obtain plasma. PRC was measured by the method described by Menard and Cate in the presence of plasma obtained from nephrectomized rats as renin substrate. PAC was determined by the radioimunoassay with a kit purchased from Dainabot Radioisotope Lab.

RESULTS

Acute Experiments

Table I summarizes mean arterial pressure, heart rate and PRC before and 3 hours after single administrations of β-adrenergic blockers. Bucumolol at 50 mg/kg p.o. significantly decreased mean blood pressure (from 163.8±6.9 to 149.4±6.7, p < 0.01, N=8) whereas propranolol at 100 mg/kg p.o. failed to do so (from 170.0±4.6 to 163.8±4.1, p > 0.05, N=9). Blood pressure increased or unchanged in 4 out of 9 animals in the propranolol group. Heart rate was significantly lowered by bucumolol but not by propranolol. PRC in the control group (N=8) tended to increase while that in bucumolol and propranolol groups decreased markedly. Table II shows the correlation between changes in PRC and changes in mean arterial blood pressure. There was a significant correlation in the bucumolol group (r=0.716, p<0.05), but not in the propranolol

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| TABLE I. Effects of Single Oral Administrations of Bucumolol and Propranolol on Mean Blood Pressure (MBP), Heart Rate and Plasma Renin Concentration (PRC) in SHR |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Water 2 ml/kg   | Bucumolol 50 mg/kg | Propranolol 100 mg/kg |
| MBP (mmHg)                     | Before 161.9±3.9| 163.8±6.9        | 170.0±4.6        |
| (mmHg)                         | After 163.1±3.4 | 149.4±6.7**      | 163.8±4.1        |
| Heart rate (beats/min)         | Before 351.3±3.4| 343.8±10.3       | 321.7±10.4       |
| (beats/min)                    | After 342.5±14.7| 303.8±5.7**      | 301.1±9.0        |
| PRC (ng/ml/h)                  | Before 3.67±0.30| 4.23±0.70        | 5.18±1.43        |
| (ng/ml/h)                      | After 4.50±1.33 | 2.53±0.63**      | 2.66±0.44*       |
| N                               | 8               | 8                | 9                |

All values are means ± S.E.
* significantly different from control value at p < 0.05.
** significantly different from control value at p < 0.01.

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group \( (r = 0.466, \ p > 0.05) \).

**Long-term Experiments**

In 3 groups of SHR aged 5 weeks (8 animal each), water (2 ml/kg), bucumolol (50 mg/kg) or propranolol (100 mg/kg) was administered by gavage once a day, and systolic blood pressure, heart rate and body weight were measured once a week. Figure 1 shows the effects of bucumolol and propranolol on the development of hypertension. In the bucumolol group, systolic blood pressure was significantly lower than that in the control group as early as 1 week after the initiation of dosing and stayed so for the remainder of the observation period. On the other hand, the difference in blood pressure between the control and propranolol groups was significant \( (p < 0.05) \) only at the 1st and 4th week. Both agents lowered heart rate throughout the 6-week observation period (Fig. 2). There was no statistically significant difference in body weight between the control group and the groups treated with \( \beta \)-adrenergic blockers (Fig. 3).

Long-term administration of bucumolol or propranolol lowered PRC (Table III), as single administrations did. Both agents tended to lower PAC, but the changes from control values were statistically not significant (Table III).

**DISCUSSION**

The present study demonstrates that both

| TABLE II. Percent Changes in Mean Blood Pressure (MBP) and Plasma Renin Concentration (PRC) following Single Administrations of Bucumolol and Propranolol, and Correlation Coefficients \( (r) \) between Them |
|---|---|---|
| MBP (%) | Water 2 ml/kg | Bucumolol 50 mg/kg | Propranolol 100 mg/kg |
| PRC (%) | 0.9±1.3 | -8.4±1.5 | -3.7±2.9 |
| \( r \) | 30.6±44.1 | -43.7±4.7 | 0.716* |
| \( N \) | 8 | 8 | 9 |

*All values are means ± S.E.*

*statistically significant at \( p < 0.05 \).

| TABLE III. Effects of Long-term Administrations of Bucumolol and Propranolol on Plasma Renin Concentration (PRC) and Plasma Aldosterone Concentration (PAC) |
|---|---|---|
| PRC (ng/ml/h) | Water 2 ml/kg | Bucumolol 50 mg/kg | Propranolol 100 mg/kg |
| PAC (pg/ml) | 4.4±0.7 | 1.9±0.3* | 2.1±0.4* |
| \( N \) | 304.4±83.5 | 226.8±57.3 | 197.6±22.8 |
| 8 | 6 | 5 |

*All values are means ± S.E.*

*significantly different from control at \( p < 0.05 \).
acute and long-term administration of bucumolol decreased blood pressure in SHR, whereas propranolol, at a dose equivalent to bucumolol in terms of β-adrenergic blocking action, was effective in lowering blood pressure only following a long-term administration. The failure of propranolol to lower blood pressure of SHR has also been reported by other authors.⁷⁻⁹ and has been attributed to a reflex vasoconstriction due to a fall in cardiac output.⁷,¹⁰

Bucumolol has been shown to be twice as potent as propranolol in β-blocking action, one third as potent in membrane stabilizing action and one tenth as potent in local anesthetic action.⁹ Therefore, at an equipotent dose in β-adrenergic blocking action, cardiodepressant action of bucumolol may be far less than that of propranolol although we did not measure cardiac output in the present study. This difference may account for the different blood pressure responses of SHR to single administrations of bucumolol and propranolol.

FIG. 1. Effects of Long-term Oral Administration of Bucumolol and Propranolol on the Development of Hypertension
Each point represents mean ± S.E. from 8 animals. Significant differences from corresponding control values (water treatment): * p < 0.05, ** p < 0.01.

FIG. 2. Effects of Long-term Oral Administration of Bucumolol and Propranolol on the Heart Rate of SHR
Each point represents mean ± S.E. from 8 animals. Significant differences from corresponding control values (water treatment): * p < 0.05, ** p < 0.01.

FIG. 3. Effects of Long-term Oral Administration of Bucumolol and Propranolol on the Body Weight of SHR
Each point represents mean ± S.E. from 8 animals.
An inhibition of renin release has been claimed to be one of the mechanisms underlying the antihypertensive action of \( \beta \)-blockers. However, not all \( \beta \)-blockers have been reported to lower plasma renin activity; e.g., propranolol\textsuperscript{11} and atenolol\textsuperscript{11} lower PRC but pindolol does not.\textsuperscript{3}

In the present study, bucumarol and propranolol significantly lowered PRC following a single administration. A significant correlation was found between changes in PRC and changes in MBP following bucumarol but not following propranolol (Table II). The reduction of PRC persisted during long-term blockade of \( \beta \)-adrenergic receptors and became even more marked (Tables I and III) despite the sustained reduction of blood pressure. These findings suggest that inhibition of renin release contributes to the antihypertensive action of bucumarol. The lack of the correlation between decreases in PRC and blood pressure in the propranolol group suggests more complicated mechanisms involved in antihypertensive action of propranolol.

PAC tended to decrease but did not decrease significantly despite the persistent decrease in PRC. A possible reason for the lack of significant decrease is that PAC is also controlled by several factors other than angiotensins concentration, e.g., by plasma Na/K balance and plasma ACTH level.\textsuperscript{12}

In addition to inhibition of renin release, two major mechanisms have been proposed for the antihypertensive action of \( \beta \)-adrenoceptor blockers: central mechanisms and reduction of cardiac output.\textsuperscript{13} The central mechanisms are unlikely in the case of bucumarol since the agent does not cross the blood brain barrier.\textsuperscript{9} Although cardio depressant action of bucumarol is expected to be far less than that of propranol as mentioned previously, it is not certain whether or not the reduction of cardiac output is involved in the antihypertensive action of bucumarol.

In conclusion, both single and long-term administrations of bucumarol decreased blood pressure in SHR, and inhibition of renin release may be, at least partly, involved in its antihypertensive action.

REFERENCES


