EFFECTS OF ECARAZINE, PRAZOSIN, PHENTOLAMINE AND HEXAMETHONIUM ON THE VASOPRESSOR REFLEXES INDUCED BY BILATERAL CAROTID ARTERY OCCLUSION AND HEAD-UP TILTING IN CATS

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In order to examine clinical potential for ecarazine, prazosin, phentolamine and hexamethonium to cause orthostatic hypotension in man, the effects of these drugs on the vasopressor reflexes induced by bilateral carotid artery occlusion (BCO) or head-up tilting (Tilt) have been investigated in gallamine-immobilized cats.

Ecarazine at doses of 0.1 to 10 mg/kg *i.v.* decreased blood pressure in a dose-dependent way whereas at 0.1 to 1 mg/kg it did not affect the pressor response to BCO or Tilt and at 10 mg/kg it suppressed only the response to BCO slightly. On the other hand, prazosin, phentolamine and hexamethonium, at hypotensive doses, not only decreased blood pressure but also inhibited pressor responses to both BCO and Tilt. Because ecarazine lacks in producing orthostatic hypotension, it seems likely that the clinical propensity of drugs to cause such side effect is correlated with the inhibition of Tilt response rather than with that to BCO. The results of comparison of the inhibition by these drugs of Tilt response indicate that ecarazine is the most favorable drug among these four drugs and that phentolamine has the highest incidence of orthostatic hypotension.

With respect to the effects of prazosin, phentolamine and hexamethonium, statistically significant correlation between the inhibition of the response to BCO and that to the compensatory reflex to Tilt has been observed. Hence it is suggested that the agents which decrease blood pressure by affecting peripheral sympathetic mechanisms might depress each efferent sympathetic pathway to the same degree.

Keywords — ecarazine; prazosin; phentolamine; hexamethonium; anti-hypertensive drug; orthostatic hypotension

INTRODUCTION

In patients receiving antihypertensive drugs, orthostatic hypotension is one of the most serious undesirable effects. Occasionally, some antihypertensive drugs, such as ganglion blocking agents, α -adrenergic blockers and adrenergic neuron blockers,^{1–3)} induce orthostatic hypotension in man. To assess the mechanism and clinical propensity of orthostatic hypotension in man, some experiments using animal models have been presented. In sinoaortic baroreceptor denervated dogs, circulatory compensatory reflex to postural changes was depressed.⁴⁾ On the other

hand, it has been reported that the depression of tilt response in animals is highly correlated with the clinical incidence of orthostatic hypotension.⁵⁾ In the present study, we comparatively examined the effects of ecarazine, prazosin, phentolamine and hexamethonium on the pressor response to tilting (Tilt) in gallamine-immobilized cats with those on the response to bilateral carotid artery occlusion (BCO).

The present study was conducted in order to investigate clinical potential for these drugs to cause orthostatic hypotension and, furthermore, to examine the correlation between Tilt and

BCO pressor responses.

MATERIALS AND METHODS

Healthy cats of either sex, weighing 1.9 to 4.1 kg, were slightly anaesthetized with 50 mg/kg of sodium thiopental (*i.p.*). After a middle incision in the cervical region, bilateral carotid arteries were dissected free of surrounding tissues in length of 3 to 5 cm to permit application and removal of occluding serrefines without stretching the arteries. The arterial blood pressure was measured with a pressure transducer (MPU-0.5, Nihon Kohden) connected to a polyethylene cannula inserted into descending aorta via the right femoral artery, and the left femoral vein was cannulated for drug injection. Heart rate was monitored from the pulse wave by a cardiometer (RT-5, Nihon Kohden).

After a surgical operation, the animal was immobilized with 20 mg/kg of gallamine triethiodide (*i.v.*) and artificially ventilated via a tracheal cannula. The experiments were started at least 2 h after the injection of thiopental in order to minimize the effect of anaesthesia on the pressor reflexes.

Each animal was supinely positioned on a specially constructed table and pressor responses to bilateral carotid artery occlusion (BCO) for 30 s and 45°C head-up tilting (Tilt) for 60 s were repeated before and after cumulative doses of drugs. Reflex response to Tilt was initiated by rapidly tilting the animal from a supine to a position 45°C from the horizontal and was cleaned 60 s later. In the preliminary experiment, tilting the animals by 30°C to 90°C caused pressor reflex responses depending upon the degrees by which they were tilted, as previously described by Doba and Reis.⁶⁾ Since 90°C head-up tilting by itself sometimes induced orthostatic hypotension in animals, we used a mild condition of 45°C head-up tilting in this experiment.

Comparison has been made between the pre-drug and post-drug values and significance of difference was assessed by paired *t*-test.

Drugs used were ecarazine hydrochloride (Apirachol®, Kyowa Hakko Kogyo), prazosin

hydrochloride (Pfizer), phentolamine mesylate (Ciba-Geigy Japan) and hexamethonium bromide (Methobromine®, Yamanouchi Seiyaku).

RESULTS

1. Control Response to BCO and Tilt

In 24 cats, resting mean blood pressure and heart rate were 164.4 ± 3.2 mmHg and 183.4 ± 6.0 beats/min, respectively. BCO produced a 54.7 ± 4.9 mmHg rise in mean blood pressure and moderately increased heart rate (Δ HR = 5.7 ± 1.0 beats/min). Tilt produced a transient decrease in blood pressure (Δ BP = -29.9 ± 2.5 mmHg), which subsequently returned rapidly to the initial level and moderately increased heart rate (Δ HR = 6.1 ± 1.1 beats/min). These changes in blood pressure and heart rate were statistically insignificant among individual groups.

2. Effects of Drugs on Blood Pressure and Heart Rate

The dose-response curves showing the effects

FIG. 1. Hypotensive Activities of Ecarazine (●), Prazosin (○), Phentolamine (■) and Hexamethonium (□) in Gallamin-immobilized Cats

Ordinate: Decrease in mean blood pressure (mmHg). Abscissa: Addition of agents (mg/kg, *i.v.*) in cumulative doses. Each point represents the mean $\pm$ S.E. of six animals.

a) $p < 0.05$, b) $p < 0.01$.

of ecarazine, prazosin, phentolamine and hexamethonium on blood pressure are indicated in Fig. 1.

Ecarazine at doses of 0.1 to 10 mg/kg *i.v.* decreased blood pressure in a dose-dependent way. Its hypotensive action was gradual in onset, the

FIG. 2. Changes in the Pressor Responses induced by Bilateral Carotid Artery Occlusion (B) for 30 s and Head-up Tilting (T) for 60 s Before and After Cumulative Doses of Ecarazine in a Gallamine-Immobilized Cat

O: Control response, 0.1 to 10: ecarazine (mg/kg, *i.v.*).

FIG. 3. Changes in the Pressor Responses induced by Bilateral Carotid Artery Occlusion (B) for 30 s and Head-up Tilting (T) for 60 s Before and After Cumulative Doses of Prazosin in a Gallamine-Immobilized Cat

O: Control response, 0.01 to 1: prazosin (mg/kg, *i.v.*).

maximal effects being achieved 30 min after the drug injection. Ecarazine at doses up to 1 mg/kg caused little change in the heart rate, while at 10 mg/kg it significantly decreased the heart rate (from 185.5 ± 13.5 to 144.3 ± 13.6 beats/min).

Intravenous injections of prazosin, phentolamine and hexamethonium promptly decreased blood pressure, the effects of them being dose-dependent. Prazosin at a higher dose of 1 mg/kg *i.v.* caused a slight but significant decrease in heart rate (from 196.3 ± 11.1 to 180.7 ± 9.6 beats/min). Phentolamine at doses of 0.1 to 1 mg/kg *i.v.* caused a slight tachycardia whereas at 10 mg/kg it slightly decreased heart rate, though these responses were statistically insignificant. Hexamethonium at a higher dose of 3 mg/kg *i.v.* caused a significant bradycardia (178.0 ± 7.1 to 135.0 ± 5.2 beats/min).

3. Effects of Drugs on the Pressor Responses induced by Bilateral Carotid Artery Occlusion (BCO)

FIG. 4. Dose-response Curves Showing the Effects of Ecarazine (●), Prazosin (○), Phentolamine (■) and Hexamethonium (□) on the Pressor Responses induced by Bilateral Carotid Artery Occlusion in Gallamine-immobilized Cats

Ordinate: Percent inhibition of the response. Abscissa: Addition of agents (mg/kg, *i.v.*) in cumulative doses. Each point represents the mean $\pm$ S.E. of six animals. a) $p < 0.05$, b) $p < 0.01$.

and Head-up Tilting (Tilt)

Typical tracings of the effects of ecarazine and prazosin are shown in Figs. 2 and 3, respectively. Ecarazine at doses up to 1 mg/kg did not affect the pressor response to BCO, but at 10 mg/kg it slightly inhibited the response to BCO. Ecarazine consistently abolished the initial fall in blood pressure caused by Tilt (BP changed from -21.7 ± 5.9 to -16.7 ± 3.1 or to -6.2 ± 2.9 mmHg at doses of 1 or 10 mg/kg) while, at all doses examined, it never affected the recovery phase of the response to Tilt. Prazosin at doses of 0.01 to 1 mg/kg inhibited pressor responses to both BCO and Tilt in a dose-dependent fashion (Figs. 4 and 5). Phentolamine and hexamethonium also inhibited both pressor responses in dose-dependent manners.

4. Correlation between the Inhibition of the Pressor Response to BCO and the Decrease in the Compensatory Reflex to Tilt

FIG. 5. Dose-response Curves Showing the Inhibition by Ecarazine (●), Prazosin (○), Phentolamine (■) and Hexamethonium (□) of the Orthostatic Tilt Responses in Gallamine-immobilized Cats

Ordinate: Inhibition of the pressor responses induced by head-up tilting (mmHg). Abscissa: Addition of agents (mg/kg, *i.v.*) in cumulative doses. Each point represents the mean $\pm$ S.E. of six animals. a) $p < 0.05$, b) $p < 0.01$.

Correlation has been examined between the inhibition of the pressor response to BCO and that to Tilt on the data obtained from the experiments on prazosin, phentolamine and hexamethonium. Statistically significant ($p < 0.01$) correlation between these two values was observed, though there was a large individual deviation (Fig. 6).

DISCUSSION

The present results show that prazosin, phentolamine and hexamethonium at their hy-

potensive doses depress the pressor responses induced by BCO and Tilt while ecarazine at its hypotensive doses apparently does not inhibit the pressor response to Tilt and little affects that to BCO. The present results in cats might be in agreement with the clinical propensity of prazosin, phentolamine and hexamethonium to cause orthostatic hypotension.^{2,3,7)}

In the present study, we have tried to examine the correlation between the inhibition by drugs of the pressor response to Tilt and that to BCO in order to clarify if efferent pathway activated by these two procedures is the same or not. Cowley *et al.*⁴⁾ reported that sinoaortic baroreceptor denervation depressed the circulatory compensatory reflex to postural changes in dogs, and suggested that the primary function of the baroreceptor reflex is to minimize variations in systemic arterial blood pressure caused by postural changes. In the present study, with respect to prazosin, phentolamine and hexamethonium, statistically significant correlation between the inhibition of the response to BCO and that to Tilt has been observed. Hence it seems likely that the agents which decrease systemic blood pressure through an interaction with peripheral sympathetic mechanisms might simultaneously depress each sympathetic pathway activated by BCO or Tilt to the same extent.

On the other hand, Antonaccio *et al.*⁵⁾ demonstrated that clonidine given either acutely or chronically in anaesthetized dogs had no effect on the pressor response to Tilt while it inhibited the response to BCO. This result suggests that Tilt might activate more parts of sympathetic pathway than BCO does. In fact, Doba and Reis⁸⁾ reported that the fastigial nucleus, triggered by vestibular mechanisms, participates in initiating and sustaining orthostatic reflexes in concert with systemic baroreceptors. Moreover, besides neural activation, catecholamine release from adrenal medulla⁹⁾ and renin release from kidney¹⁰⁾ are also reported to be involved in the tilting pressor reflexes. In this respect, the inhibition of the pressor response to Tilt seems to be the better index of orthostatic hypotension in

FIG. 6. Correlation between the Inhibition of the Pressor Response to Bilateral Carotid Artery Occlusion and that to Head-up Tilting in Gallamine-immobilized Cats

Each point was determined by all of the data obtained from the experiments of prazosin, phentolamine and hexamethonium. Linear regression equation is: $y = 0.47x - 3.85$, $r = 0.53$ ($p < 0.01$) Percent inhibition of the pressor response to bilateral carotid artery occlusion is represented by x and decrease in pressor response (mmHg) to head-up tilting is represented by y .

TABLE. I. *Hypotensive Activities and Reflex Circulatory Response to Tilt at Corresponding Hypotensive Doses in Gallamine-immobilized Cats*

Compounds	ED ₃₀ ^{a)}	PH ₃₀ ^{b)}
Ecarazine	2.64 ± 1.06 ^{c)}	0.17 ± 3.7
Prazosin	(2.25 ± 0.31) × 10 ⁻²	-25.0 ± 6.8* ^{d)}
Phentolamine	2.47 ± 1.86	-28.8 ± 2.6** ^{d)}
Hexamethonium	1.13 ± 0.17	-23.8 ± 6.2* ^{d)}

a) The dose (mg/kg, i.v.) which decrease mean blood pressure by 30 mmHg.

b) The change in the pressor response to Tilt (mmHg) at the dose which decrease mean blood pressure by 30 mmHg.

c) Values are presented as mean ± S.E. of 6 animals.

d) Statistically significant difference (*: $p < 0.05$, **: $p < 0.01$).

man than the inhibition of BCO pressor reflex.

In the present study, it was observed that the initial fall in blood pressure induced by Tilt was consistently prevented by ecarazine whereas the late phase of compensation was unaffected. Although we cannot explain the involved mechanism of the prevention by ecarazine of hypotension caused by Tilt, it might potentiate the early phase of compensation. Thus, the lack of orthostatic hypotension in man is in agreement with the present results.

Finally, the propensity of these drugs to cause orthostatic hypotension in man was estimated by examining the inhibition of Tilt response by these drugs at doses which lower mean blood pressure by 30 mmHg (Table I). If this estimation is reasonable, ecarazine might be the most favorable drug among these drugs and prazosin, phentolamine and hexamethonium can be anticipated to cause orthostatic hypotension, with the highest incidence of orthostatic hypotension for phentolamine. This estimation, however, could be true for the case of acute treatments with drugs and the chronic administration might elicit different situations, as it was reported that tolerance to orthostatic hypotension develops in the repeated treatment of patients with prazosin.³⁾

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