Effects of Dihydroergotamine and Etilerine on Experimentally-Induced Postural Hypotension in Dogs

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The effects of dihydroergotamine and etilefrine on experimentally-induced postural hypotension were examined. Although dihydroergotamine at 3 and 10 μg/kg (i.v.) increased blood pressure (BP), it did not affect cardiac output (CO). However, dihydroergotamine at 10 μg/kg reduced the decrease in CO induced by the tilt. Therefore, it is suggested that the increase in BP is induced by the contraction of resistance vessels, and that the inhibition of the decrease in CO due to tilt is induced by the contraction of capacity vessels.

Etilerine at 0.1 mg/kg (i.v.) increased BP and heart rate (HR), however it did not attenuate the decrease in BP induced by the tilt. Although it tended to increase CO, it did not attenuate the decrease in CO. It is suggested that the increase in BP is due to the contraction of resistance vessels, and to the increase in cardiac contractile force and HR.

In this study, dihydroergotamine and etilefrine did not attenuate the decrease in BP due to tilt, though dihydroergotamine inhibited the decrease in CO due to tilt. As an explanation, it is suggested that dihydroergotamine induces contraction of resistance vessels as well as capacity vessels, however the effects of the drug on resistance vessels is weak, and that etilefrine has little or no effect on capacity vessels. In our previous study, midodrine, an alpha-1 agonist, attenuated the decreases in BP and CO due to tilt, and it has been suggested that the inhibition was induced by the contraction of capacity vessels. Therefore, dihydroergotamine, etilefrine and midodrine show different pharmacological profiles in experimentally-induced postural hypotension.

Keywords — postural hypotension; cardiovascular parameter; vasoconstrictor; dihydroergotamine; etilefrine; midodrine

Introduction

The shift of body posture from a lying position to a standing position causes cardiovascular adjustment which tends to compensate for the effects of gravity on the circulatory system. However, some patients with impaired compensatory mechanisms show orthostatic hypotension. It is thought that the blockade of the sympathetic nervous systems reduces venous return, resulting in decreased cardiac output (CO), and consequently a decrease in blood pressure (BP).

In the present study, we have produced experimentally-induced postural hypotension using hexamethonium (20 mg/kg s.c.) administration and 30°-tilt in anesthetized dogs.1) The hypotension was stable for at least the first 60 min after the administration of hexamethonium. In our previous study, midodrine, (±)-2-amino-N-(2,5-dimethoxy-β-hydroxyphenethyl)acetamide hydrochloride, was found to effectively reduce experimentally-induced postural hypotension by increasing CO as a result of increased venous return to the heart via the venous contraction induced by postjunctional alpha-1 adrenoceptors.1–3)

Therefore, we examined the effects of two different vasoconstrictors, dihydroergotamine and etilefrine on experimentally-induced postural hypotension by focusing the effects of these drugs on CO, which indirectly shows venous function, in order to compare these drug’s effects with midodrine’s effects, already reported.1,2)

Materials and Methods

Measurement of BP and Heart Rate (HR)

— Mongrel dogs of either sex (8.5—14 kg) were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Each animal was placed in a supine
position on a specially constructed table and ventilated artificially through an endotracheal tube with room air at a tidal volume of 20 ml/kg at 18—20 breaths/min with a Sinano-respirator (SN-408, Tokyo, Japan). Femoral arterial pressure was measured with a pressure transducer (Nihon Kohden MPU-0.5, Tokyo, Japan) connected to a rigid polyethylene tube inserted into the left femoral artery. The pressure transducer was positioned so that its zero reference point was always at the heart level. The HR was measured using a HR counter (Nihon Kohden AT-600G) triggered by the pressure pulse waves.

**Measurement of Vertebral Blood Flow (VBF) and CO** — VBF, as a measure of cerebral blood flow, was measured with a flow probe connected to an electromagnetic flowmeter (Nihon Kohden MFV-2100) in the vertebral artery. CO was measured with a flow probe attached to the aortic arch.

**Experimentally-Induced Postural Hypotension** — Postural hypotension in the dog was induced by treatment with a combination of administration of a ganglion-blocking agent, hexamethonium (20 mg/kg s.c.), and 30°-tilt. The head-up position was maintained for 1 min at 10 min intervals. Measurements were made 30 s after the initiation of the tilt. The first tilt was made 20 min after administration, and the second one was made 10 min later. The value obtained for the second tilt was taken as the control value. Details of the experimental method have been reported previously. 1

**Materials** — The following drugs were used: hexamethonium bromide (Tokyo Kasei, Japan), dihydroergotamine tartrate (Tokyo Kasei) and etilefrine hydrochloride (in ampule; Boehringer Ingelheim). Hexamethonium was dissolved in 0.9% saline and administered subcutaneously. Dihydroergotamine was dissolved in a 20% dimethyl sulfoxide solution. Dihydroergotamine and etilefrine were injected intravenously via a cannula inserted into the left femoral vein.

**Analysis** — The values of hemodynamic parameters before, and 10 or 30 min after administration of the drug were analyzed using the Student’s paired t-test. The change of the basal value induced by the tilt before administration of the drug was analyzed using the Student’s paired t-test. The degrees of BP, HR, VBF and CO changes induced by the tilt before, and 10 or 30 min after administration of the drug were analyzed using the Student’s paired t-test.

**Results**

**Hypertensive Effects of Vasoconstrictors**

The hypertensive effects of dihydroergotamine and etilefrine are summarized in Table I. An intravenous injection of dihydroergotamine at doses of 3 and 10 μg/kg significantly raised BP. Etilefrine at a dose of 0.1 mg/kg significantly raised basal BP. The amplitudes of the increase in BP induced by dihydroergotamine at a dose of 10 μg/kg and etilefrine at a dose of 0.1 mg/kg were about the same.

**Pharmacological Actions of Dihydroergotamine on the Experimentally-Induced Postural Hypotension**

In comparison with the control, neither VBF nor CO was affected by an intravenous injection of dihydroergotamine 3 μg/kg. Dihydroergotamine did not affect the changes in BP, VBF or CO induced by the tilt (Fig. 1).

On the other hand, an increased dose of dihydroergotamine at 10 μg/kg significantly attenuated the decrease in systolic BP induced by the tilt 30 min after administration. VBF 10 min after administration, in comparison with the control, was raised by dihydroergotamine, but the agent did not affect the changes in VBF induced by the tilt. Although CO was not affected by dihydroergotamine, the decrease in CO produced by the tilt was significantly attenuated by it (Fig. 2).

**Table I. Hypertensive Effects of Dihydroergotamine and Etilefrine on Mean BP in Anesthetized Dogs at 10 and 30 min after Intravenous Administration**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>N</th>
<th>BP change (ΔmmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 min</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>3 μg/kg</td>
<td>5</td>
<td>12.0±2.3a</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>10 μg/kg</td>
<td>5</td>
<td>38.0±8.0b</td>
</tr>
<tr>
<td>Etilefrine</td>
<td>0.1 mg/kg</td>
<td>5</td>
<td>29.8±6.3a</td>
</tr>
</tbody>
</table>

Variables are given as the mean ± S.E.M. N represents the number of experiments. a) p<0.05, b) p<0.01 compared with control.
Pharmacological Actions of Etilerine on the Experimentally-Induced Postural Hypotension

An intravenous injection of etilefrine at 0.1 mg/kg did not affect the changes in BP induced by the tilt. HR was significantly increased by etilefrine. VBF and CO showed a tendency to increase, but the changes of VBF and CO induced by the tilt were not affected by it (Fig. 3).

Discussion

The present study shows the effects of dihydroergotamine and etilefrine, which are frequently used in the treatment of hypotensive diseases, on experimentally-induced postural hypotension. In our previous studies, midodrine, an alpha-1 adrenoceptor agonist, was shown to attenuate the decrease in BP, CO and cerebral blood flow in dogs with experimentally-induced postural hypotension. The effects of midodrine are thought to constrict the venous beds, resulting in an increase of venous return to the heart, and consequently, an increase in CO. Therefore, we focused on the effects of other vasoconstrictors, dihydroergotamine and...
etilefrine, on CO and BP in experimentally-induced postural hypotension.

It has been demonstrated that dihydroergotamine induces the contraction of vascular smooth muscle by the stimulation of alpha-adrenoceptors. In an animal study, dihydroergotamine was shown to contract the capacitance vessels preferentially, rather than the resistance vessels, thereby preventing venous pooling. In a clinical study, Nordenfelt and Mellander reported that dihydroergotamine has beneficial effects in patients with orthostatic hypotension, by raising CO, stroke volume and central blood volume. Conte et al. demonstrated that dihydroergotamine prevented postural hypotension due to the administration of ganglion blocking agents by redistributing the circulating blood and increasing the venous return to the heart. These results support the results of the previous animal experiments. However, some doubts about the effectiveness of dihydroergotamine were reported in the clinical study.

In the present study, we used doses of dihydroergotamine and etilefrine which induced almost the same degree of hypertension as midodrine, in order to compare the effects of dihydroergotamine and etilefrine on experimentally-induced postural hypotension with that of midodrine. This study showed that although dihydroergotamine exerted hypertensive effects, it did not significantly attenuate the decrease in BP induced by the tilt. However, midodrine attenuated the decrease in BP induced by the tilt.

In the resting state, dihydroergotamine at 3 \( \mu \text{g/kg} \) did not significantly affect CO. However, at 10 \( \mu \text{g/kg} \), the drug tended to reduce CO, suggesting that the high dose of this drug constricts peripheral arteries. In the tilt condition, dihydroergotamine significantly attenuated the decrease in CO produced at 10 \( \mu \text{g/kg} \) (Fig. 2), but not significantly at 3 \( \mu \text{g/kg} \). It is conceivable that the inhibition of the decrease in CO induced by the tilt is induced by the contraction of capacitance vessels. Therefore, it is thought that a dose of 10 \( \mu \text{g/kg} \) of dihydroergotamine acts on resistance vessels as well as capacitance vessels like midodrine at 0.3 mg/kg. As the reason why dihydroergotamine did not inhibit the decrease of BP induced by the tilt, which was inhibited by midodrine, it is considered that the effect of dihydroergotamine on resistance vessels is weaker than that of midodrine. Since dihydroergotamine and midodrine have attenuated the decrease of CO induced by the tilt, systemic circulatory blood flow would be maintained in the tilt condition. However, midodrine has attenuated the decrease of BP induced by the tilt, so the drug probably caused the contraction of the arterioles, which were strongly regulated by the sympathetic nervous system. As we have already reported, midodrine did not affect cerebral
or coronary blood flow.\textsuperscript{11)} In humans, it was demonstrated that sympathetic neurogenic regulation of cerebral\textsuperscript{12)} and coronary\textsuperscript{13)} blood flow was lower than that of other vascular beds, and that cerebral and coronary vascular beds were strongly regulated by metabolic effects. Therefore, as midodrine effectively inhibited the decrease of cerebral blood flow induced by the tilt in dogs,\textsuperscript{12)} the drug may slightly constrict arterioles except cerebral and coronary arteries, and the blood flow which the drug attenuates the decrease of CO may be distributed in vital organs (cerebrum and heart) in the tilt condition of humans.

It is well known that etilefrine increases the contractile force of heart muscle, CO, and stroke volume.\textsuperscript{14–17)} The venous return to the heart,\textsuperscript{16)} and BP, are increased by increasing the circulating blood volume.\textsuperscript{14–17)}

In the present study, a hypertensive effect was shown to be induced by etilefrine. It is suggested that the hypertensive effect is related to the contraction of resistance vessels by the stimulation of alpha-adrenoceptors,\textsuperscript{13)} and is also related to the increase in cardiac contractile force and HR by the stimulation of the beta-adrenoceptors.\textsuperscript{14–17)} Etilerfine tended to increase the VBF and CO, which can be explained by the increases in HR and the contractile force. In this study, etilefrine did not inhibit the change of the parameter induced by the tilt. This suggests that etilefrine has little or no effects on venous vessels.

The hypertensive effects of dihydroergotamine and etilefrine are shown in Table I. Since midodrine significantly increased BP, even 30 min after the administratio of the drug,\textsuperscript{1,2)} the duration of the hypertensive action of dihydroergotamine and etilefrine was shorter than that of midodrine. The reason for the long duration of action of midodrine is related to the fact that the drug is a prodrug, gradually releasing an active metabolite, ST-1059, by hydrolyzing glycine from midodrine in the liver.\textsuperscript{18,19)}

In conclusion, dihydroergotamine and etilefrine did not attenuate the decrease in BP induced by the tilt in this study, whereas dihydroergotamine attenuated the decrease in CO induced by the tilt, which indicates that this drug constricts capacitance vessels. Etilerfine did not change hemodynamic parameters due to the tilt, which indicates that the drug has little or no effects on capacitance vessels. Considering those data together with the data from a previous study dealing with midodrine action, this study demonstrates the different pharmacological profiles of dihydroergotamine, etilefrine and midodrine in experimentally-induced postural hypotension.

References


