EFFECT OF CEREBRAL CIRCULATORY DRUGS ON CEREBRAL AND PERIPHERAL CIRCULATION, WITH SPECIAL REFERENCE TO AMINOPHYLLINE, PAPAVERINE, CYCLANDELATE AND ISOXSUPRINE

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Various kinds of cerebral circulatory drugs are widely used in the treatment of cerebral vascular diseases. It is indispensable that the effect is appropriate for clinical application theoretically and experimentally, since each drug has its own pharmacological characteristic.

In this study, the hemodynamic effect of several cerebral circulatory drugs (aminophylline, papaverine, cyclandelate and isoxsuprine) on cerebral and peripheral circulation was investigated by means of a newly devised ultrasonic Doppler apparatus, which is capable of multiple and simultaneous blood flow measurement non-operatively and continuously in man in situ.

METHODS

The blood flow change in the internal carotid artery and brachial artery was investigated in each subject by means of the new Doppler apparatus devised by the author before, during and after the administration of the drugs as follows. Aminophylline (250 mg), papaverine (40 mg) and cyclandelate (12.5 mg) dissolved in 10 to 20 ml of 5% glucose solution were intravenously administered. On the other hand, isoxsuprine (10 mg) was intramuscularly administered. The change of heart rate was also simultaneously investigated by means of the Heart Rate Tachometer. Fig. 1 shows the block diagram of the apparatus, which consists of the ultrasonic Doppler flowmeter and the on-line data processing system. Fig. 2 shows a scene of the experiment.

RESULTS

1. Circulatory effect of aminophylline (Fig. 3)

A biphasic blood flow pattern was induced in the internal carotid artery by intravenous aminophylline, i.e., conspicuous and sustained decrease of blood flow during the administration and con-

![Fig. 1a. Block diagram of ultrasonic flowmeter.](image-url)

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spicuous and transient increase of blood flow after the administration. On the other hand, a slight and shortly sustained increase of blood flow was observed in the brachial artery. The heart rate was moderately increased.

2. Circulatory effect of papaverine (Fig.4)
A conspicuous and transient increase of blood flow in the internal carotid artery and slight and shortly sustained increase of blood flow in the brachial artery were induced by papaverine intravenous administration. The heart rate was generally unaltered.

3. Circulatory effect of cyclandelate (Fig.5)
A moderate and prolonged increase of blood flow in the internal carotid artery with no alteration of blood flow in the brachial artery was induced by intravenous cyclandelate administration. The heart rate was generally unaltered.

4. Circulatory effect of isoxsuprine (Fig.6)
A general increase of blood flow in the brachial artery with no alteration of blood flow in the internal carotid artery was induced by intramuscular isoxsuprine throughout the experiment (around thirteen minutes). The heart rate was also generally increased.

**DISCUSSION**

1. Circulatory effect of aminophylline
Much information regarding this problem has been presented as follows.

The following two theories related to cerebral circulation are presented, i.e., cerebral vasoconstriction theory\(^a\) vs. cerebral vasodilation theory\(^b\). Of these, the former theory is more widely accepted. However, according to the author's study by means of the ultrasonic Doppler technique, the circulatory effect of aminophylline on cerebral circulation is dependent upon the administration time, i.e., cerebral vasoconstric-

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Fig. 3. Effect of aminophylline on cerebral and peripheral circulation.

Fig. 4. Effect of papaverine on cerebral and peripheral circulation.

tion during administration and cerebral vasodilation after administration. In the present study, a biphasic blood flow pattern was observed in the internal carotid artery as well as in the previous study. As for the pulmonary circulation and coronary hemodynamics, there seem to be indefinite and complicated results, depending upon the clinical situation of the subjects, i.e., pulmonary artery pressure and both ventricular end-diastolic pressures increase consistently, heart rate and cardiac output are unaltered or increase according to the pathophysiological situation of heart diseases. In the present study, a moderate increase in heart rate was observed.

The peripheral circulation also seems to be similar to the pulmonary circulation and coronary hemodynamics, i.e., blood pressure is unaltered or increased according to the pathophysiological situation of heart diseases.

In this study, the following antipodal circulatory response was observed between the cereb-
Fig. 5. Effect of cyclandelate on cerebral and peripheral circulation.

Fig. 6. Effect of isoxsuprine on cerebral and peripheral circulation.

Although the vasodilatory effect of papaverine is prominent, its organ specificity to cerebral vessel is not so prominent, i.e., papaverine affects the peripheral vessel as well as the cerebral vessel. In addition, the duration of its vasodilation is comparatively short. On the other hand, papaverine gives rise to positive chronotropic and inotropic effects on the heart.

In this study, the vasodilatory effect of papaverine in the internal carotid artery was more potent than that in the brachial artery. A dura-
tion of vasodilation, however, was very short. Therefore, the above result generally coincided with results of others.

3. Circulatory effect of cyclandelate

Cyclandelate induces an increase of blood flow due to primary vasodilation similar to papaverine. Organ specificity, however, to the cerebral vessel and duration of vasodilation are more prominent in the case of cyclandelate than with papaverine. In addition, cyclandelate gives rise to negative chronotropic and inotropic effects on the heart. It is suggested, therefore, that cyclandelate is more appropriate for treatment in the elderly cerebrovascular patients accompanied by cardio-vascular diseases. 10, 11

In this study, the vasodilatory effect of cyclandelate was more potent in the internal carotid artery than in the brachial artery. In addition, the duration of the vasodilation in the internal carotid artery was conspicuously longer compared to papaverine. That is, the result was completely coincident with the results of others.

4. Circulatory effect of isoxsuprine

Isoxsuprine is one of the adrenergic β-receptor stimulators and it is widely used as a cerebral and peripheral vasodilator. 10, 11

Ahlquist 12 has suggested the presence of α- and β-receptors, located in the adrenergic system. There seems to be a conspicuous difference as to the localization and response between the two receptors as follows.

α-receptor is localized mainly in the skin, kidney, etc. On the other hand, the β-receptor is localized mainly in the coronary system, skeletal muscle, etc. In addition, vasoconstriction in the skin and kidney is induced by α-receptor stimulation. Vasodilation in the coronary system and skeletal muscle is induced by β-receptor stimulation. β-receptor stimulation, moreover, gives rise to positive chronotropic and inotropic effects on the heart.

It is suggested that isoxsuprine induces vasodilation and increase of blood flow in the extremity, and acceleration of the heart, since isoxsuprine belongs to the group of β-receptor stimulators. It may be concluded, therefore, that caution must be exercised when administering isoxsuprine in the elderly patients.

In this study, the following results were observed, i.e., gradual increase of blood flow in the brachial artery and increase in heart rate. That is, the results were generally coincident with the concept presented by Ahlquist.

SUMMARY

The hemodynamic effect of several cerebral circulatory drugs (aminophylline, papaverine, cyclandelate and isoxsuprine) on cerebral and peripheral circulation was investigated by means of the new ultrasonic Doppler apparatus devised by the author simultaneously, non-operatively and continuously in man in situ. The circulatory mechanism of these drugs was discussed based on the obtained results.

REFERENCES


