CIRCULATORY EFFECT OF SEVERAL CEREBRAL CIRCULATORY DRUGS IN MAN, WITH SPECIAL REFERENCE TO AMINOPHYLLINE, PAPAVERINE, CYCLANDELATE, VINCAMINE, PROSTAGLANDIN E₁ 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 characteristics.

The present author has devised the on-line Doppler ultrasonic apparatus which is capable of simultaneous blood flow measurement noninvasively and continuously in man in situ.

The circulatory effect of some cerebral circulatory drugs, i.e., aminophylline, papaverine, cyclandelate and isoxsuprine, on heart rate and cerebral and brachial blood flow was investigated by means of the on-line Doppler ultrasonic technique, as a clinical application of this method.

In the present study, the circulatory effect of several cerebral circulatory drugs, i.e., aminophylline, papaverine, cyclandelate, vincamine, prostaglandin E₁ and isoxsuprine, on heart rate and cerebral and brachial blood flow as well as blood pressure which is one of the important circulatory factors, was investigated by means of this technique and the obtained results were compared with those of the previous experiment.

MATERIALS AND METHODS

The subjects were 33 apparently healthy males over 60 years of age.

Key Words:
Off-line and on-line doppler Ultrasonic technique

Blood flow changes in the internal carotid artery and brachial artery were investigated in each subject by means of the on-line Doppler ultrasonic apparatus devised by the author before, during and after the administration of the following cerebral circulatory drugs, simultaneously and continuously: aminophylline (250 mg), papaverine (40 mg), cyclandelate (112.5 mg), vincamine (10 mg) and prostaglandin E₁ (100 μg), were dissolved in 10 to 20 ml of distilled water, and administered intravenously, isoxsuprine (10 mg) was administered intramuscularly.

Alterations in heart rate and systolic blood pressure were simultaneously investigated by means of the Heart Rate Tachometer for heart rate measurement and Shimizu's Continuous Systolic Monitor for systolic blood pressure measurement.

It has been shown by Yoshida that the blood flow change in the internal carotid artery, measured by the Doppler ultrasonic technique, was in proportion to the cerebral blood flow change measured by 133Xe clearance method.

RESULTS

(1) Circulatory effect of aminophylline (Fig. 1)

A similar circulatory alteration was induced by intravenous aminophylline in all of 5 subjects.

A biphasic blood flow response was induced in the internal carotid artery by intravenous aminophylline, i.e., conspicuous and sustained decrease of blood flow from during to a short time after the administration, and conspicuous but transient increase of blood flow around 1 to

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2 minutes after the administration.

A slight and shortly sustained increase of blood flow was observed in the brachial artery, and heart rate and systolic blood pressure were generally unaltered.

(2) Circulatory effect of papaverine (Fig. 2)

A similar circulatory alteration was induced by intravenous papaverine in all of 5 subjects. A conspicuous but 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 intravenous

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Circulatory Effect of Several Cerebral Circulatory Drugs in Man

Circulatory Effect of Cyclandelate

Heart Rate

Systolic Blood Pressure

Brachial Artery

Internal Carotid Artery

\[ \Delta BF(\%) : \text{Changing rate of blood flow} \]

Fig. 3.

Circulatory Effect of Vincamine

Heart Rate

Systolic Blood Pressure

Brachial Artery

Internal Carotid Artery

\[ \Delta BF(\%) = \text{Changing rate of blood flow} \]

Fig. 4.

papaverine.

Heart rate and systolic blood pressure were generally unaltered.

(3) Circulatory effect of cyclandelate (Fig. 3)

A similar circulatory alteration was induced by intravenous cyclandelate in all of 5 subjects.

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.

Heart rate and systolic blood pressure were generally unaltered.

(4) Circulatory effect of vincamine (Fig. 4)
A generally similar circulatory alteration was induced by intravenous vincamine in all of 5 subjects.

A conspicuous and prolonged increase of blood flow in the internal carotid artery with no alteration or slight increase of blood flow in the brachial artery was induced by intravenous treatment.

Circulatory Effect of Several Cerebral Circulatory Drugs in Man

Circulatory Effect of Prostaglandin E₁

Heart Rate

Systolic Blood Pressure

Brachial Artery

Internal Carotid Artery

△BF (%): Changing rate of blood flow

Fig. 7.

Circulatory Effect of Isoxsuprine

Heart Rate

Systolic Blood Pressure

Brachial Artery

Internal Carotid Artery

△BF (%): Changing rate of blood flow

Fig. 8.

vincamine.

Heart rate was decreased and systolic blood pressure was generally unaltered.

(5) Circulatory effect of prostaglandin E₁

Circulatory effect of prostaglandin E₁ was investigated in 8 subjects.

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Alteration of blood flow in the internal carotid artery varied with intravenous prostaglandin E₁ as follows. (i) No alteration of blood flow--4 subjects (Fig. 5). (ii) Slight decrease or increase of blood flow--2 subjects each (Fig. 6, 7).

Heart rate and blood flow in the brachial
artery were slightly or moderately increased, and
systolic blood pressure showed a slight and shortly
sustained decrease.

(6) Circulatory effect of isoxsuprine (Fig. 8)

A generally similar circulatory alteration was
induced by intramuscular isoxsuprine in all of 5
subjects.

Gradual and conspicuous increase of blood
flow in the brachial artery and heart rate was
induced by intramuscular isoxsuprine.

No alteration or slight increase of blood flow
in the internal carotid artery and no alteration of
systolic blood pressure were observed.

DISCUSSION

The on-line Doppler ultrasonic technique is
the most advantageous for the clinical evaluation
of cerebral circulatory drugs, since the technique
is capable of multiple and simultaneous measure-
ment of several circulatory factors such as cere-
bral and peripheral blood flow, heart rate and
blood pressure, non-invasively and continuously
in man in situ.2–9

(1) Circulatory effect of aminophylline

Much information regarding this problem has
already been presented.

The following two theories related to cerebral
circulation are presented, i.e., cerebral vaso-
constriction theory11 vs. cerebral vasodilation
theory.12 Of these, the former theory is more
widely accepted.

However, according to the author’s study by
means of the off-line13 and on-line2 Doppler
ultrasonic techniques, the circulatory effect of
aminophylline of cerebral circulation is dependent
upon the administration time, i.e., cerebral vaso-
constriction from during to a short time after the
administration and cerebral vasodilation around
1 to 2 minutes after administration.2,13

As for the mechanism of cerebral blood flow
change in aminophylline administration, the
direct effect of the drug toward the cerebral
vessel (vasoconstriction or vasodilation) should
be considered, since the alterations in blood
depression and blood flow in both arteries did not
coincide quantitatively and phasically.

The effect of aminophylline on heart rate and
blood pressure is generally said to be as follows.14
Heart rate is unaltered or increased and blood
pressure is unaltered or decreased. The experi-
mental result of the present study was coincident
with the above finding, i.e., heart rate and systolic
blood pressure generally unaltered.

On the other hand, the following antipodal
circulatory response was observed between
cerebral and brachial blood flow during intra-
venous aminophylline, i.e., decrease of blood
flow in the internal carotid artery and increase of
blood flow in the brachial artery. It is suggested,
therefore, that aminophylline belongs to the
category of a vasodilator associated with cerebral
vasoconstriction classified by Fazekas.1

(2) Circulatory effect of papaverine, cyclande-
late and vincamine

Papaverine and cyclandelate have been most
widely used clinically as general vasodilators
whose effect is due to primary vasodila-
tion.1–2,13,15,16

In the previous study,2 it was testified that
although the cerebral vasodilatory effect of
papaverine was more potent than cyclandelate,
organ specificity of papaverine for the cerebral
vessel and duration of cerebral vasodilation was
less prominent than with cyclandelate.

In the present study, the vasodilatory effect
of papaverine on the internal carotid artery was
more potent than that on the brachial artery.
The duration of vasodilation, however, was very
short. Therefore, it is suggested that intravenous
drip is most appropriate compared to single-shot
administration of papaverine.

On the other hand, the vasodilatory effect of
cyclandelate on the internal carotid artery was
not so potent as that of papaverine. The duration
of vasodilation, however, was conspicuously
longer compared to papaverine. The vasodilatory
effect of cyclandelate on the brachial artery was
slight or nil, if any.

Alteration of heart rate and blood pressure
with the administration of papaverine and cy-
clandelate was conspicuously slight. It is sug-
gested, therefore, that papaverine and cyclande-
late are appropriate for treatment in cerebrovas-
cular patients accompanied by cardiovascular
diseases.

Although much clinical information regarding
the cerebral vasodilatory effect of vincamine has
been presented in Europe, the circulatory effect
of the drug in man seems to be inadequate.

As for the circulatory effect of vincamine,
findings similar to those with papaverine and
cyclandelate administration were observed, i.e.,
conspicuous and prolonged increase of blood
flow in the internal carotid artery, no alteration
or slight increase of brachial blood flow, decreased
heart rate and generally unaltered systolic blood
pressure.

It is suggested, therefore, that vincamine is as

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advantageous for treatment in the elderly cerebrovascular patients with cardiovascular diseases as papaverine and cyclandelate.

As for the mechanism of cerebral blood flow change with papaverine, cyclandelate and vinca-mine, the direct effect of the drugs toward the cerebral vessel (vasodilation) should be considered, since the alterations in blood pressure and blood flow in both arteries did not coincide quantitatively and phasically.

(3) Circulatory effect of prostaglandin \( E_1 \)

As for the cerebral circulatory effect of prostaglandin \( E_1 \), antipodal findings are presented, according to the experimental difference, i.e., cerebral vasoconstriction theory\(^{17}\) vs. vasodilation theory\(^{18}\).

In the present study, the following three findings were observed. (i) No alteration of cerebral blood flow-4 subjects. (ii) Slight increase of cerebral blood flow-2 subjects. (iii) Slight decrease of cerebral blood flow-2 subjects.

It is suggested, therefore, that the cerebral circulatory effect of prostaglandin \( E_1 \) varies according to the individual cerebrovascular reactivity.

On the other hand, heart rate and brachial blood flow were increased, and systolic blood pressure showed a slight and shortly sustained decrease.

These findings coincide well with the results of experiments conducted with the pressure-velocity hysteresis technique\(^{19}\).

As for the mechanism of vascular reactivity to prostaglandin \( E_1 \) by the internal carotid artery and brachial artery, a primary vascular reactivity (vasoconstriction or vasodilation) may be considered, since the alterations in blood pressure and blood flow in both arteries did not coincide quantitatively and phasically. In conclusion, the circulatory effect of prostaglandin \( E_1 \), especially the cerebral circulatory effect, should be further investigated.

(4) Circulatory effect of isoxsuprine

Isosuprine is one of the adrenergic \( \beta \)-receptor stimulators and is widely used as a cerebral and peripheral vasodilator\(^{15,16}\).

Ahquist\(^{20}\) has suggested the presence of \( \alpha \)-and \( \beta \)-receptors, located in the adrenergic system. There seems to be a conspicuous difference between the two receptors as follows: \( \alpha \)-receptor is localized mainly in the cutaneous and splanchnic vessel, and \( \beta \)-receptor is localized mainly in the muscular and coronary vessel, etc.

Vasoconstriction in the cutaneous and splanchnic vessel is induced by \( \alpha \)-receptor stimulation. On the other hand, vasodilation in the muscular and coronary vessel is induced by \( \beta \)-receptor stimulation. \( \beta \)-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 (increase of heart rate and cardiac output), since isoxsuprine belongs to the group of \( \beta \)-receptor stimulators. The above concept was supported by the previous study\(^2\).

In the present study, findings similar to the previous study\(^2\) were obtained, i.e., conspicuous increase of brachial blood flow and heart rate with no alteration or slight increase of cerebral blood flow and no alteration of systolic blood pressure. The absence of change in the systolic blood pressure compared to the conspicuous increase of heart rate may be due to a compensatory increase of cardiac output against the peripheral vasodilation. In conclusion, it is suggested that caution should be exercised when administering isoxsuprine in the elderly patient with cardiovascular disorders.

**SUMMARY**

Circulatory effects of several circulatory drugs, aminophylline, papaverine, cyclandelate, vincamine, prostaglandin \( E_1 \) and isoxsuprine, on cerebral blood flow (blood flow in the internal carotid artery), brachial blood flow, heart rate and systolic blood pressure were investigated by means of the on-line Doppler ultrasonic technique in 33 apparently healthy males over 60 years of age, simultaneously and continuously in situ.

(1) A biphasic cerebral blood flow response was induced by intravenous aminophylline, i.e., conspicuous and sustained decrease of blood flow from during to a short time after the administration, and conspicuous but transient increase of blood flow around 1 to 2 minutes after the administration.

(2) A conspicuous but transient increase of cerebral blood flow was induced by intravenous papaverine.

(3) A moderate or conspicuous and prolonged increase of cerebral blood flow was induced by intravenous cyclandelate and vincamine.

(4) Alteration of cerebral blood flow varied with intravenous prostaglandin \( E_1 \) as follows. (i) No alteration of blood flow-4 subjects. (ii) Slight decrease or increase of blood flow-2 subjects each.

(5) No alteration or slight increase of cerebral blood flow was induced by intramuscular isoxsuprine.

(6) The findings coincide well with those obtained previously.

REFERENCES


