The Effect of Intracarotid Aminophylline Infusion on the Cerebral Circulation

BY U. GOTTSTEIN, M.D.,* AND O. B. PAULSON, M.D.†

Abstract: The influence of aminophylline infusion into the internal carotid artery on cerebral blood flow (CBF) was studied in 12 patients. Six of them were studied using the N₂O saturation technique of Kety and Schmidt, and the other six using the Xenon-133 intra-arterial injection method of Lassen and Ingvar. Intracarotid infusion of aminophylline resulted in a significant decrease of CBF. Previous studies have shown that aminophylline also reduced CBF when injected intravenously. Furthermore, in the present study it was demonstrated that a small dose of aminophylline which was without cerebral vasoconstricting effect when infused intravenously still reduced CBF when infused into the internal carotid artery. Thus aminophylline is a cerebral vasoconstrictor due to a local action on the cerebral vessels.

Additional Key Words: cerebral blood flow, Kety-Schmidt method, vasoconstrictor, Xenon-133 intra-arterial injection method

Ten to 20 years ago aminophylline was used in the treatment of stroke in many countries because it was believed that this drug was a cerebral vasodilator (see review in 1). By using quantitative methods for measuring cerebral blood flow (CBF) in man, especially with Kety and Schmidt's N₂O-method, it was later demonstrated that CBF decreases after aminophylline.¹⁻⁶ These new results were confirmed by other authors with different methods,⁶ and recently also with the Xenon-133 method of Lassen and Ingvar for measuring regional and total CBF.⁷ Subsequent animal studies using the same method but in a modification with Krypton-85 also confirmed the vasoconstrictor effect of aminophylline.⁷⁻⁸ Concomitant analyses of the cerebral metabolic rate of oxygen and of glucose, before and after administration of aminophylline, had shown that both metabolic values remained constant while CBF decreased.¹⁻² Thus the effect of aminophylline was similar to that of mild hyperventilation.¹⁻⁷

The mechanism by which aminophylline constricts the cerebral vessels is still unknown. One of us (U.G.) suggested that induced hyperventilation might be of major importance for the vasoconstrictor effect of aminophylline.¹ This concept is supported by studies in artificially ventilated cats demonstrating that aminophylline injected into the vertebral artery leads to a brief cerebral vasodilation.¹ Further, no peripheral vasoconstricting drug, so far known, leads to a significant cerebral vasoconstriction when injected intravenously.¹⁻⁰ In the human, the effect of intravenously injected aminophylline, however, seems to have a more pronounced cerebral vasoconstrictor effect than corresponding to the slight reduction of PᵃC⁰₂ due to hyperventilation.¹⁻⁷ The present study was undertaken to further clarify the mechanism of action of aminophylline. Aminophylline was infused in man directly into the internal carotid artery during the flow measurements in order to get a maximal cerebral hemispheric effect and at the same time to minimize the systemic and brain stem (respiratory) effect.

Methods

Two studies were performed using different methods and different doses of aminophylline.
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One of us (U.G.) used the Kety and Schmidt N₂O-saturation method,¹⁰⁻¹² and the other (O.B.P.) used the Xenon-133 intracarotid injection technique of Lassen and Ingvar.¹³,¹⁴ In the first-mentioned study larger doses of aminophylline were used than in the other study.

1: STUDIES USING THE KETY AND SCHMIDT N₂O-SATURATION METHOD

The modification of Scheinberg¹¹ and Bernsmeier¹² was used. Six patients with headache and dizziness were studied (cases 1 to 6). The femoral artery and the superior bulb of the internal jugular vein were punctured under local anesthesia. A mixture of N₂O in atmospheric air was inhaled for ten minutes, during which time blood samples were drawn from the mentioned vessels. The CBF was calculated from the N₂O concentrations in the blood samples. In addition a small needle was introduced into the internal carotid artery and used for infusion of saline or aminophylline.

The CBF was first measured in the resting state during which isotonic saline was infused into the internal carotid artery. Thirty minutes after the end of the first measurement (end of N₂O inhalation) an intracarotid aminophylline infusion was started and maintained for ten minutes. At the sixth minute of infusion a second measurement of CBF was undertaken lasting the next ten minutes (N₂O inhalation for ten minutes). The dose of aminophylline infused was 12 mg per minute in the first three patients (cases 1 to 3) and 24 mg per minute in the other three patients (cases 4 to 6) (table 1).

During each flow measurement a sample of arterial and jugular venous blood was collected for the determination of the oxygen and the carbon dioxide concentrations using Van Slyke’s technique.

The cerebral metabolic rate of oxygen was calculated as CBF X arteriovenous oxygen difference.

The arterial blood pressure was measured by auscultation during each CBF measurement.

2: STUDIES USING THE XENON-133 INTRACAROTID INJECTION TECHNIQUE OF LASSEN AND INGVAR

Six patients with presenile dementia were studied (cases 7 to 12). The modification of the Xenon-133 method used has been described previously in detail¹⁴ and shall be briefly summarized here. A small polyethylene catheter was placed in the internal carotid artery by means of the Seldinger technique and later used for an angiographical study. Xenon-133 (2 to 3 mCi) dissolved in 2 to 3 ml of isotonic saline was injected rapidly (1 or 2 seconds) through the catheter into the internal carotid artery, and the clearance of the isotope was followed by 35 small scintillation detectors placed externally over the ipsilateral hemisphere.

The cerebral blood flow was calculated as the...
mean of the flow values from all 35 regions. From a single clearance curve the flow was calculated from the initial part of the clearance curve as:

\[ \text{rCBF}_{\text{initial}} = 2 \times D_{\text{initial}} \text{ ml/100 gm/min.} \]

2 is the product of the conversion factor \( \ln 10 \approx 2.30 \) from base 10 to natural logarithm and of the tissue to blood partition coefficient for Xenon-133 of the gray matter taken to be 0.87. \( D_{\text{initial}} \) is the initial slope of the logarithmically recorded clearance curve in percent of decade per minute. All flow values were corrected for remaining activity from previous Xenon-133 injections.14

A time interval of 15 minutes was allowed between each flow measurement, i.e., between each Xenon-133 injection.

The CBF was first measured during the resting state. Two measurements were performed in order to secure adequate steady state in all cases, and good reproducibility was observed as reported previously.14 Thereafter the CBF was measured during infusions of aminophylline either into the internal carotid artery through the indwelling catheter or into a brachial vein. The aminophylline infusion in the cases of intracarotid infusion was started one and one-half to two minutes before the Xenon-133 injection, and in the cases of intravenous infusion it was begun two to two and one-half minutes before the injection. In both conditions the infusion was maintained throughout the first two minutes after the Xenon-133 injection during which the clearance of the isotope was followed. The doses of aminophylline infused were 20 mg per minute in the first two cases (cases 7 and 8) and 2.5 mg per minute in the other four cases (cases 9 to 12). The sequence of infusions and CBF measurements are given in table 2. Furthermore, the CBF was measured 15 minutes following the last aminophylline injection.

During each flow measurement a sample of blood was collected for determination of the carbon dioxide tension (\( \text{PaCO}_2 \)). The mean arterial blood pressure (MABP) was measured using an electric manometer.

**Results**

1: STUDIES USING THE KETY AND SCHMIDT \( \text{N}_2 \)-SATURATION METHOD

During the intracarotid aminophylline infusion cerebral blood flow decreased in all except one patient (case 1), where it was unchanged (table 1, fig. 1). The decrease was statistically significant (\( p < 0.02 \)).

In three patients (cases 1 to 3), in whom 12 mg of aminophylline were infused per minute, CBF decreased an average of 4.4

**Table 2**

| Case no. | Flow before | Flow after | CBF (ml/100 gm min) | Time from inner carotid artery to \( ^{3} \text{H} \) labeled aminophylline \( ^{3} \text{H} \) labeled aminophylline | Aminophylline infused
|---------|-------------|-------------|---------------------|---------------------------------------------------------------------------------|-----------------------------
| 1       | 36.0        | 20.0        | 4.0                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 20 mg per minute            |
| 2       | 35.0        | 24.0        | 1.0                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 20 mg per minute            |
| 3       | 30.0        | 15.0        | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 20 mg per minute            |
| 4       | 25.0        | 10.0        | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 10 mg per minute            |
| 5       | 20.0        | 9.0         | 1.1                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 10 mg per minute            |
| 6       | 15.0        | 3.0         | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 7.5 mg per minute           |
| 7       | 10.0        | 5.0         | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 2.5 mg per minute           |
| 8       | 5.0         | 3.0         | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 2.5 mg per minute           |
| 9       | 15.0        | 10.0        | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 7.5 mg per minute           |
| 10      | 10.0        | 5.0         | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 2.5 mg per minute           |
| 11      | 5.0         | 3.0         | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 2.5 mg per minute           |
| 12      | 15.0        | 10.0        | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 7.5 mg per minute           |
| 13      | 10.0        | 5.0         | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 2.5 mg per minute           |
| 14      | 5.0         | 3.0         | 1.5                | 30 min after \( ^{3} \text{H} \) labeled aminophylline injected                    | 2.5 mg per minute           |

*Injection time four minutes.*

In these patients the intravenous infusion was performed 15 minutes before the intracarotid infusion and 15 minutes before the flow following aminophylline infusion.
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Studies using the Kety-Schmidt technique are illustrated in the left diagram and those using the Xenon-133 technique in the right diagram. In both diagrams the flow values before aminophylline infusion are given in the left part, and those during the aminophylline infusion in the right part. A flow reduction is observed during aminophylline infusion. The mean flow changes are indicated by the thick lines.

ml/100 gm/min, or 7%, and there was no significant change of arterial CO₂ concentration or of mean arterial blood pressure. In the other three patients (cases 4 to 6), in whom 24 mg of aminophylline were infused per minute, CBF decreased an average of 9.8 ml/100 gm/min, or 22%; the arterial carbon dioxide concentration decreased 2.3 vol %, or 5.8%, and the mean arterial blood pressure decreased 13 mm Hg, or 11%.

The cerebral metabolic rate of oxygen (CMRO₂) was unchanged during the aminophylline infusion (table 1).

2: STUDIES USING THE XENON-133 INTRACAROTID INJECTION TECHNIQUE OF LASSEN AND INGVAR

Cerebral blood flow decreased in all cases during the intracarotid aminophylline infusion (tables 2 and 3, fig. 1). This decrease was statistically significant (p < 0.001) if the flow values both were or were not corrected for small deviations due to the small changes of PaCO₂ (4% CBF change per mm Hg PaCO₂ change).

In five of the six patients studied a CBF measurement was repeated 15 minutes after the last aminophylline infusion. These flow values were still low although somewhat increased as compared to those observed during the intracarotid infusion. Thus the vasoconstrictor effect of aminophylline is of a rather long duration and not confined only to the period of the intracarotid infusion.

In the last four patients studied a small dose of 2.5 mg aminophylline per minute was used for the infusion. This dose was infused intravenously as well as into the internal carotid artery at different times. Cerebral blood flow decrease was observed only after intracarotid infusion. The CBF values measured during the intravenous infusion were unchanged as compared to those during the previous CBF measurement which was performed either in the resting state (cases 9 and 10) or during the intracarotid infusion (cases 11 and 12). These data suggest that aminophylline has a direct effect on the cerebral circulation within the carotid distribution.

Discussion

During recent years several studies on the

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pathophysiology of stroke have shown that vasodilators may be harmful in the treatment of acute stroke. Furthermore, the possibility has been discussed that vasoconstrictors might have a beneficial effect. In view of these considerations the cerebral action of aminophylline seems interesting as this drug previously was believed to be a cerebral vasodilator, whereas later on it has been shown that aminophylline in fact is a cerebral vasoconstrictor.

This result was very surprising, and it could be assumed that the decrease of cerebral blood flow (CBF) after aminophylline injections was due to a nonspecific action, e.g., hyperventilation. Therefore, in the present study we investigated the effect of aminophylline by infusing it in different doses directly into the internal carotid artery in man. It was confirmed that aminophylline acts as a cerebral vasoconstrictor and reduces CBF even after the infusion of very small doses into the carotid artery. Also, we could confirm that this effect cannot be ascribed to a small PaO₂ decrease only, since the CBF reduction was much more marked than would correspond to the small PaO₂ fall observed. In several cases PaCO₂ even remained constant (tables 1 and 2).

The present study demonstrates in addition that a small dose of aminophylline, which was without effect when infused intravenously, still reduced CBF when infused into the internal carotid artery (Tables 2 and 3). Therefore, aminophylline must have a direct vasoconstricting effect on the cerebral circulation as, e.g., papaverine has a vasodilating effect. In our present knowledge of the physiology of the cerebral circulation no centers controlling the CBF are known. Important physiological regulatory mechanisms of the cerebral vasomotor function, such as the effect of the tissue pH, are well known to be localized in or around the cerebral vessels. Therefore, it might be suggested that the vasoconstrictor effect of aminophylline also is due to a local action on the cerebral vessels. The real mechanism of action of aminophylline, however, remains still unknown. It might be that aminophylline changes the extracellular pH or potassium concentration, but other mechanisms might also be involved.

References

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