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THE EFFECTS OF INTRAVENOUSLY ADMINISTERED AMINOPHYLLINE ON CEREBRAL CIRCULATION AND METABOLISM IN MAN¹

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There is a widely held belief that aminophylline, in addition to its effect on bronchioles, kidneys and heart, also exerts a stimulating effect on central nervous function and improves the cerebral circulation (1, 2). Experimental evidence for this belief is difficult to find. Practically none has been reported in humans and very little in animals. Dumke and Schmidt (3) demonstrated that the cerebral vessels are dilated by the intra-arterial injection of aminophylline in the anesthetized macaque monkey. Intravenous aminophylline, on the other hand, increased cerebral blood flow in two monkeys and decreased it in another two. Thus, the cerebral actions of aminophylline as it is used clinically are not clearly defined and it seemed of interest, therefore, to study the effects on the cerebral circulation and metabolism in man.

METHODS

Ten hospitalized patients, without any obvious cerebral depression, were chosen at random. There were six females and four males varying in age from 14 to 69 years. A cerebral blood flow (CBF) was performed by means of the nitrous oxide method (4). This was called the control flow (C). Following this, 0.5 G. of aminophylline in 250 cc. of physiological saline solution were administered intravenously over a period of 20 minutes. While the last 50 cc. ran in, a second or experimental cerebral blood flow (E) was performed. Pulse, mean arterial blood pressure (MABP), obtained directly from the femoral artery by means of a damped mercury manometer, and respiratory rates were recorded before and during each flow. Cerebral metabolic rate in terms of cerebral O₂ consumption (CMR_{O₂}) and cerebrovascular resistance (CVR) were calculated as previously described (4).

Blood gas analyses were made with the Van Slyke-Neill manometric apparatus (5). Measurement of blood pH was made anaerobically at 37° C. by means of a glass electrode and a Cambridge potentiometer. Values for

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blood carbon dioxide tension were calculated by means of the nomograms presented by Peters and Van Slyke (5).

RESULTS

The data obtained in these studies are presented in Tables I and II. The most striking result was a statistically significant decrease in cerebral blood flow from a mean of 59.4 to 44.4 cc./100 G./min. ($p < .01$). This decrease in CBF was due to a highly significant increase in cerebrovascular resistance from 1.7 to 2.1 mm. Hg ($p < .001$). An expected increase in respiration occurred, reflected in a decrease in arterial CO₂ tension and an increase in arterial pH. There was no significant change in arterial O₂ content, MABP or cerebral metabolism in the group as a whole. As a result of the decrease in CBF and the constant cerebral O₂ utilization, the internal jugular O₂ content decreased from 8.2 to 6.2 vols. % ($p < .001$) and the cerebral arteriovenous O₂ difference increased from 6.7 to 8.7 vols. % ($p < .01$). The internal jugular CO₂ content, pH and CO₂ tension remained constant.

The high values obtained for the control cerebral blood flow (mean of 59.4 compared to a normal mean of 51 cc./100 G./min.) were probably due to the presence of anemia in several of these unselected hospital patients. This is shown by the mean hematocrit of 38%.

DISCUSSION

The mechanism for these changes is not immediately apparent. It is possible that aminophylline stimulates respiration leading to hyperventilation with a low arterial CO₂ tension. Since CO₂ is a known dilator of cerebral vessels, the decrease in arterial CO₂ tension causes cerebral vasoconstriction with consequent increase in cerebrovascular resistance and decrease in cerebral blood flow (6). However, the decrease in arterial

TABLE I
Effects of aminophylline on blood gases

Pt.	Age	Sex	MABP		Hct.	Arterial								Internal Jugular							
						O ₂ Content		CO ₂ Content		CO ₂ Tension		pH		O ₂ Content		CO ₂ Content		CO ₂ Tension		pH	
						mm. Hg		%		mm. Hg		%		C		E		mm. Hg		%	
J. T.*	54	M	83	83	44	17.0	17.3	46.2	45.3	41	38	7.38	7.40	9.6	6.6	54.3	55.5	55	56	7.31	7.32
A. P.	38	F	81	81	29	11.3	10.9	50.2	48.3	40	37	7.40	7.41	6.1	4.0	55.1	53.9	49	49	7.35	7.34
M. G.	69	M	112	107	48	18.4	15.9	49.8	50.3	44	45	7.39	7.38	9.6	8.3	57.7	58.4	59	61	7.31	7.30
E. M.	64	F	108	95	33	12.3	12.0	46.6	44.7	33	30	7.46	7.48	5.0	3.9	53.6	53.1	45	44	7.38	7.39
J. W.*	31	F	95	81	38	13.9	14.3	57.5	54.7	52	46	7.35	7.40	9.0	6.1	62.8	62.9	62	58	7.30	7.34
W. R.	19	M	85	85	43	17.1	17.0	53.0	50.7	50	43	7.34	7.39	11.5	9.7	58.4	58.4	58	59	7.32	7.31
C. P.	45	F	92	96	42	16.9	17.5	52.2	50.5	44	38	7.40	7.46	9.3	7.3	60.2	60.9	59	59	7.33	7.34
S. W.	66	M	95	102	33	16.8	16.9	48.1	46.9	43	39	7.38	7.40	8.4	6.4	56.1	57.1	54	55	7.32	7.32
H. C.*	25	F	78	80	33	12.3	12.7	43.8	41.5	—	—	—	—	6.0	4.2	50.1	50.3	—	—	—	—
L. S.*	25	F	96	95	34	12.9	13.7	50.7	47.6	42	40	7.38	7.38	7.4	5.0	56.3	56.2	54	58	7.32	7.29
Mean			92.5	90.5	38	14.9	14.8	49.8	48.1†	43.2	39.6†	7.39	7.41	8.2	6.2†	56.5	56.7	55.0	55.4	7.33	7.33

* These patients showed subjective reactions to aminophylline.

† Indicates statistically significant change ($p < 0.01$).

C = Control Flow.

E = Experimental Flow following aminophylline.

TABLE II
Effects of aminophylline on cerebral function

Pt.	Cerebral							
	A-V _{O₂}		CBF		CMR _{O₂}		CVR	
	C	vols. % E	C	cc./100 G./min. E	C	cc./100 G./min. E	C	mm. Hg cc./100 G./min. E
J. T.*	7.4	10.7	44	39	3.2	4.2	1.9	2.1
A. P.	5.2	6.9	73	47	3.8	3.6	1.1	1.7
M. G.	8.8	7.6	46	42	4.0	3.2	2.5	2.6
E. M.	7.3	8.1	46	39	3.4	3.2	2.3	2.4
J. W.*	4.9	8.2	80	54	3.9	4.4	1.2	1.5
W. R.	5.6	7.3	81	43	4.5	3.2	1.1	1.9
C. P.	7.6	10.2	52	32	4.0	3.2	1.8	3.1
S. W.	8.4	10.5	44	35	3.7	3.7	2.2	2.9
H. C.*	6.3	8.5	59	51	3.7	4.3	1.3	1.6
L. S.*	5.5	8.7	69	62	3.8	5.4	1.4	1.5
Mean	6.7	8.7†	59.4	44.4†	3.8	3.8	1.7	2.1†

* These patients showed subjective reactions to aminophylline.

† Indicates statistically significant change ($p < 0.01$).

C = Control Flow.

E = Experimental Flow following aminophylline.

CO₂ tension is probably not large enough to produce the decrease in cerebral blood flow observed after aminophylline. From observations during voluntary hyperventilation (6) it appears that a decrease in arterial pCO₂ of greater magnitude would be necessary to produce the degree of cerebral vasoconstriction which occurred with aminophylline.

It is perhaps more probable that aminophylline constricts the cerebral vessels and thus causes the decrease in cerebral blood flow. With the decrease

in cerebral flow, CO₂ tension of the brain would be expected to increase. Since increased CO₂ tension is a known respiratory stimulant, it may be postulated that the cause of the hyperventilation resides in the diminished cerebral blood flow. This hyperventilation diminishes the arterial CO₂ tension and results in a drop of the brain and internal jugular CO₂ tension to its previous level.

With the decrease in cerebral blood flow however achieved, and a constant overall O₂ consumption, the internal jugular O₂ content, of course,

falls. Since the internal jugular O_2 content is a reflection of the brain O_2 content, aminophylline causes anoxia of cerebral tissue.

The decrease in cerebral blood flow following aminophylline is compatible with the observations of Greene, Paul and Feller (7) that this drug decreases cerebrospinal fluid pressure. Other compatible results are those of Gibbs and his associates (8) who found that 0.5 G. caffeine sodium benzoate injected intravenously resulted in a drop in cerebral blood flow as measured qualitatively by a thermoelectric flow recorder. Caffeine has been shown to decrease cerebrospinal fluid pressure (9, 10). As a result of independent spinal fluid pressure and cerebral blood flow studies with high and low CO_2 tensions (6, 11), and with histamine (12) it is now apparent that cerebral vasoconstriction decreases cerebrospinal fluid pressure while vasodilation tends to raise it.

It was noted that four of the patients reacted to the drug with extreme anxiety associated with symptoms such as tachycardia, palpitation, dizziness, sweating, weakness, nausea, an intense desire to void, and a drop in blood pressure. Each of these four cases had an increase in cerebral O_2 consumption (see Table II), the mean showing a statistically significant rise from 3.7 to 4.6 cc./100 G./min. None of the other six patients showed an increase in $CMRO_2$. These six had a statistically significant decrease in cerebral O_2 consumption from 3.9 to 3.3 cc./100 G./min.

In those patients who experienced anxiety and an increase in cerebral metabolism, aminophylline may primarily have caused the associated symptoms by its effect on the heart, blood pressure or kidneys. These symptoms may then have caused the anxiety which in turn could have led to the increase in cerebral metabolism. It is equally possible that aminophylline may have increased cerebral metabolism and that this primary increase resulted in the anxiety and some of the associated symptoms.

SUMMARY

1. The effects of administration of clinically therapeutic doses of aminophylline were studied on the blood gases, blood pH, cerebral blood flow, cerebral O_2 consumption, and cerebrovascular

resistance in ten hospitalized patients without any obvious cerebral depression.

2. In these cases aminophylline produced a marked constriction of cerebral vessels and a real anoxia of cerebral tissue.

3. Some patients react to the drug with pronounced anxiety associated with disturbing symptoms and an increase in cerebral O_2 consumption.

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