Effects of Methyl Alcohol on Cerebral Blood Flow and Metabolism

Observations During and After Acute Intoxication

LOUIS L. BATTEY, M.D., Augusta, Ga.
JOHN L. PATTERSON Jr., M.D., Richmond, Va.
and
ALBERT HEYMAN, M.D., Durham, N. C.

Methyl alcohol and its toxic metabolic products exert their severest and most destructive effects upon the structure and function of nerve tissue. Depression or derangement of cerebral function is present to some degree in almost every patient with methanol intoxication, with symptoms ranging from headache and confusion to profound coma.* Impairment of optic nerve function is also commonly found, manifested by disturbances varying from transient amblyopia to permanent and total blindness.

Heretofore, observations on the physiological abnormalities produced in the brain by methyl alcohol have been limited to studies on experimental animals. The 1951 outbreak of methanol poisoning in Atlanta provided an opportunity for the measurement of the cerebral blood flow and oxygen consumption in several of these patients. This paper reports the findings in five cases during or soon after the acute phase of the disorder and includes follow-up studies on four of these persons.

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From the Departments of Physiology and Medicine, Emory University School of Medicine, and Medical Service of Grady Memorial Hospital, Atlanta. Present addresses: 1407 Gwinnett St., Augusta, Ga. (Dr. Battey); Department of Medicine, Medical College of Virginia, Richmond, Va. (Dr. Patterson); Department of Neurology, Duke University School of Medicine, Durham, N. C. (Dr. Heyman).

*References 1 and 2.

Material and Methods

Full details of the outbreak of poisoning have been reported elsewhere by Cooper and associates,[2] and only a brief description is given here. During the week beginning Oct. 21, 1951, a total of 323 patients who had ingested bootleg whisky were seen at Grady Memorial Hospital. Analysis of samples of this concoction showed 35% to 40% methyl alcohol by weight and 2% to 4.5% ethyl alcohol. Patients in acute intoxication exhibited variations of the characteristic clinical picture, with depressed sensorium, delirium, loss of consciousness, and visual disturbances. Severe abdominal pain, vomiting, dyspnea, and headache were among the most prominent symptoms. A fatal result followed the reported ingestion of as little as 1 oz. (30 cc.) of the mixture, while another patient survived the ingestion of 1 pt. (500 cc.). There were 41 deaths. The deaths which occurred while the patient was under observation appeared to be respiratory in nature, with cardiac activity persisting after cessation of respiration.

Four of the five patients subjected to cerebral studies were below 40 years of age, and the fifth was 63 years old. Three of the group had a history of moderate hypertension. They had ingested from 1 oz. to 1 pt. of the contaminated whisky. On admission to the hospital, four of the subjects were stuporous and irrational, and one was comatose. Initial studies were done within two days following the onset of symptoms, at which time the sensorium was clear in four of the patients. Coma persisted in the fifth patient, who died four days after the initial cerebral blood flow measurement. All had received sodium bicarbonate, most of it intravenously, prior to the initial studies. The dose of the alkali averaged 70 gm. in the four patients who survived; 140 gm. in two days was given to the patient who died (Case 5). Case 5 also received corticotropin by intravenous drip. Acidosis, as suggested by reduced arterial CO_2, was still present in two patients.

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Each of the five patients had marked visual impairment on admission. Three of them showed impairment in visual acuity at the time of the initial blood flow procedure. One patient had total loss of vision, which persisted throughout his hospitalization.

Follow-up studies were done approximately one week later on the four surviving patients, at which time the acidosis had subsided and mental changes had improved. Ophthalmoscopic evidence of optic nerve damage and retinal edema had diminished, but visual impairment was still present in every patient.

The cerebral blood flow (CBF) was studied by the nitrous oxide method of Kety and Schmidt[3] with the slight modifications previously described.[4] The cerebral oxygen consumption (CMR_2) was obtained from the CBF multiplied by the arteriovenous oxygen difference. The cerebral vascular resistance was obtained from the mean arterial pressure, measured with a damped mercury manometer, divided by the cerebral blood flow. The blood oxygen and carbon dioxide were determined by the combined procedure for the analysis of both gases on a single sample, as described by Peters and Van Slyke.[5]

Results

The individual and mean values for the cerebral functions measured during acute methanol intoxication and a week later, in convalescence, are given in the accompanying Table. These are compared with mean values obtained from a group of 15 normal subjects of comparable mean age and age distribution. Three of these control subjects were between the ages of 60 and 65; the remainder were less than 45 years of age. Values for statistical significance are given, although it is realized that the number of patients is small for this type of analysis.

Cerebral blood flow was decreased appreciably in each patient during the stage of acute intoxication and ranged from 30 to 42 cc/100 gm. brain/min. The mean value of 35 cc. was 30% below the normal mean of 50 cc/100 gm/min. One week later there was increase in flow in two of the four surviving patients, amounting to 8 and 15 cc/100 gm/min. in Cases 2 and 1, respectively. However, the mean value still remained 14% below normal. This decrease in blood flow was associated with a rise in cerebral vascular resistance. The CVR in each patient was above the normal mean of 1.8 mm. Hg/cc. blood flow/100 gm. brain/min. The mean of the group was 72% greater than normal. Following treatment, the CVR showed an appreciable fall in only one of the four surviving patients. Mean arterial blood pressures were slightly lower during the stage of acute intoxication than during convalescence.

The oxygen utilization of the brain ($CMRO_2$) was markedly decreased in each patient during acute intoxication, the average for the group being 30% below the control value of 3.0 cc/100 gm. brain/min. During convalescence the cerebral oxygen consumption increased markedly in two patients and very slightly in the other two patients. The mean value still remained 13% below normal.

The arterial CO_2 content during acute intoxication was greatly reduced. Unfortunately, pH determinations could not be obtained, so that values for arterial CO_2 tension could not be calculated. Values for hemoglobin and hematocrit were increased in all cases during acute intoxication, probably as a result of dehydration. Mean values for arterial oxygen saturation were slightly below control values during intoxication and were little changed at the time of the follow-up procedure.

Clinical examination six months after intoxication revealed complete blindness with bilateral optic trophy in one patient (Case 3) and marked loss of vision in two other patients (Cases 1 and 4). No other sequalae were noted. One patient (Case 2) did not return for further study. Repeat physiological studies in Case 3 showed continued depression of cerebral oxygen consumption, with values of 2.5 cc/100 gm/min. three weeks and, again, eight months after the intoxication. The

Case	Sex	CBF Cc./100 Gm./Min.		CMRO₂ Cc./100 Gm./Min.		CVR Mm.Hg/ Cc./100 Gm./Min.		(A-V)O₂ Mm. Hg		Mean Art. Pressure Mm. Hg		H'crit, %		Hgb Gm./100 Cc.	Art. CO₂ mM/Liter		Cerebral R.Q.		Approx.* Amt. Methanol Ingested	Ven. CO₂ (on Adm.) mM/Liter	Clinical Status*		
		I†	III†	I	II	I	II	I	II	I	II	I	II		I	II	I	II			Admission	I	II
1 34	F	35	50	1.4	2.4	3.1	2.2	3.9	4.9	109	111	41	34	12.3	19.7	20.2	0.89	0.80	½ pt.	9	D,R,N, V4+,A	Alert,O, V+	Alert,O,P, N,V+
2 26	M	38	41	1.8	2.5	2.6	2.4	4.7	6.1	99	97	48	38	16.1	13.9	22.4	0.74	0.66	1 oz.	13	L,D,R,N, V4+,A	Alert,R,N, V2+,A	Alert,O,R, V3+
3 40	M	30	38	2.6	2.8	3.8	3.9	8.7	7.4	115	147	41	39	13.0	4.9	22.9	0.85	0.86	½ pt.	15	D,R,N, V4+	O,L,R,N, V4+	Alert,P,R, N,V4+
4 37	M	42	42	2.3	2.5	1.9	2.4	5.5	5.9	80	100	41	34	14.7	17.9	24.2	0.99	0.77	2 oz.	4.5	L,R,N, V4+,A	L,N,V2+, A	Alert,N, V2+
5 63	F	31	....	2.2	....	3.9	....	7.1	....	120	....	40	..	12.6	25.6	....	0.93	..	½ pt.	8	C,R,N,A, Hk; did not re-spond	C,R,N	Died 4th day after Procedure I‡
Mean of first four		36	43	2.0	2.6§	2.9	2.7	5.7	6.1	101	114	43	36	14.0	14.1	22.4	0.87	0.77					
Mean of five		35‖	....	2.1‖	....	3.1‖	....	6.0	....	105 ¶	....	42	..	13.7	16.4	....	0.88	..					
Mean of controls		50	....	3.0	....	1.8	....	6.1	....	89	....	39	..	11.3									

* Clinical status: O=oriented; L, lethargic; D, disoriented; C, comatose; P, pupillary changes; R, retinal edema; N, optic nerve changes; V, visual defect (1+, 2+, 3+, 4+); A, acidosis; Hk, hypokalemia.

† I, on admission; II, follow-up.

‡ Autopsy findings: Cerebral edema and congestion; pulmonary edema, mild; acute necrosis of pancreas; congestion of G. I. tract, liver, and kidneys.

§ Significance of difference from mean of procedure I $=0.1>P>0.05$.

‖ Significantly different ($P<0.01$) from mean in 15 control subjects of the same age range.

¶ $P<0.05$.

cerebral blood flow was slightly increased at eight months, the value being 41 cc/100 gm/min.

Comment

An interesting feature of the results was the failure of the cerebral oxygen consumption during the acute stage of methanol intoxication to correlate well with the existing clinical picture or with the prognosis of the individual patient. The two patients with the lowest values for cerebral metabolism (Cases 1 and 2) had only slight mental changes and survived. The comatose patient (Case 5), who later died, had a somewhat higher value for cerebral metabolism. Similar lack of correlation between the $CMRO_2$ and the mental state has also been found in uremia,[6] the explanation for which is not clear in either case.

Several factors may be responsible for the observed increase in cerebral vascular resistance following methanol ingestion, the most important of which would seem to be cerebral edema. Varying degrees of cerebral edema and hyperemia were found in all the autopsied cases of the Atlanta mass poisoning. This marked interstitial edema of the brain, combined with arterial and capillary damage with resultant swelling, would doubtless produce a diminution in the caliber of the vascular bed and a consequent reduction in cerebral blood flow.

Although the pH of the blood could not be measured in these patients, there is little doubt that it was reduced, at least in the patients with lowered blood CO_2 content. At the present time the effect of changes in pH on cerebral blood flow are the subject of controversy. Kety and his associates[7] believed that a decrease in pH was responsible for the increased blood flow observed in their cases of diabetic acidosis. However, recent studies by Schieve and Wilson[8] and observations on 10 subjects in this laboratory † have shown that cerebral blood flow is either reduced or not affected by the acidosis induced by intravenous administration of ammonium chloride. On the basis of his observations, Schieve suggested that regulation of cerebral blood flow is more closely dependent on CO_2 tension than on pH. Acidosis, as suggested by a definitely reduced blood CO_2 content, while present in all of our patients on admission, existed in only two of them during the initial blood flow determinations and was absent a week later, at the time of follow-up studies. It appears doubtful, therefore, that change in pH was an important factor in the reduction in cerebral blood flow observed in our series.

It is reasonable to assume that the arterial CO_2 tension, at least in the patients with low blood CO_2 content, was reduced below normal. The acidosis would bring about a conversion of blood bicarbonate to carbonic acid. Hyperventilation under the stimulus of the acidemia would be expected to continue until the arterial pCO_2 was reduced below normal, and the ratio of dissolved to bound CO_2 in the plasma returned toward normal. A primary reduction in arterial pCO_2 has been shown to be a cerebral vasoconstrictor stimulus.[9] In diabetic acidosis arterial pCO_2 is markedly reduced; yet for some reason blood flow is only slightly reduced in the milder cases and is actually increased in coma.[7]

The very significant decrease in cerebral oxygen consumption found in acute methanol poisoning is in keeping with certain earlier observations. Leaf and Zatman[10] reported that formaldehyde and formate, both of which are metabolic products of methanol, depress the metabolism of ox retina, but that methanol itself is without effect. Roe[11] has stated that formic acid inhibits cell respiration by binding the ferment iron in the cells and that this reaction is increased in the

† Patterson, J. L., Jr., and Heyman, A.: Unpublished observations.

presence of acidosis. Gradinesco[12] demonstrated that methanol first causes excitability and then diminution in nerve response, resulting eventually in complete absence of nerve function. Additional observations on the toxic properties of methanol are reviewed by Bennett and colleagues.[13]

Our studies confirm the hypothesis that the oxidative processes of cerebral cells are impaired in acute methanol intoxication. It appears unlikely that the reduction in cerebral blood flow alone could account for this decrease in metabolism, since both functions were reduced to the same degree. The normal brain tolerates a 21% reduction in blood flow, for a short time at least, without depression of metabolism.[14] A significant decrease in arterial oxygen content was not found in any of our patients and therefore was not instrumental in reducing the oxygen utilization by the brain. Rather, it would seem to have resulted from some more direct action of the toxic by-products of methanol, foremost of which is formic acid, and presumably also formaldehyde.

Summary

1. In five patients with acute methanol intoxication, both the mean cerebral blood flow and the oxygen consumption were reduced 30% below the normal values. One week later, these functions in four surviving patients were only 14% below normal.

2. The degree of depression of cerebral metabolism correlated poorly with the reported amount of methanol ingested. The patient who died had a higher initial level of cerebral oxygen consumption than did two patients who survived.

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