Zeitschrift: Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: 3 (1947-1948)

Heft: 2-3

Artikel: Methanol poisoning

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DOI: https://doi.org/10.5169/seals-306893

D. C. 615.9:615.74

Methanol Poisoning

By **Oluf Røe, Oslo**

During World War II there were very many cases of poisoning with methanol (methyl alcohol) in Norway. A study of 82 cases in hospitals in Oslo and the neighbourhood resulted in findings somewhat at variance with conventional opinions in this field. In what follows I have given an account of some of the most important conclusions to which clinical investigations have led.

To those of us who have had the opportunity to observe several such cases it is obvious that there is very little difference in the clinical picture from case to case, provided there are no complications.

The very long latent period, which is generally some 18 hours, is characteristic of this form of poisoning. The first manifestations of it are lassitude, anorexia, nausea and a giddiness which is often troublesome. Vomiting becomes gradually more frequent and violent, being associated with very severe abdominal pain which is usually situated in the epigastrium and is of a colicky character. There is also often violent pain in the back and limbs. When these severe manifestations have set in, they are always associated with Kussmaul's respiration, slight cyanosis, and reduction of vision to the extent of amaurosis. The pupils are dilated, and their reaction to light is weak or completely absent. The patient becomes mentally confused, drowsy and even comatose. Shortly before his death, his dyspnœa gives place to apnœa. His pulse, which for some time has been powerful and only a little more rapid than normal, becomes rapid and soft just before death.

It is obvious that nearly all these manifestations of methanol poisoning are due to acidosis which was first demonstrated (1921) by *Harrop* and *Benedict*, who attached great importance to it.

Subsequently, the disagreement of most other observers with this opinion is undoubtedly due to failure to demonstrate severe acidosis in experimental animals poisoned by methanol. It is in particular the experiments on dogs carried out in 1922 by *Haskell* and his associates which have given rise to the belief that acidosis does not play any important part in this matter. Some of their dogs died even when the

alkali reserve was normal. Other dogs, showing a slight or moderate degree of acidosis, recovered. Treatment with bicarbonat had no beneficial effect.

In man, however, investigations have shown that the degree of acidosis is not only of importance, but is of quite vital significance to the issue of every case. All the 24 patients admitted to hospital with a slight or moderate degree of acidosis were found to possess normal vision although many of them had drunk large quantities of methanol. The 48 patients with severe acidosis (alkali reserve under 26 vols.%) suffered, with only three exceptions, from amblyopia or amaurosis. The three patients whose vision was unimpaired, showed an alkali reserve just under 26 vols.%. When the alkali reserve is measured shortly before death, it is as a rule about 10 vols.%, and death is evidently due to acidosis.

In conformity with the belief that acidosis is of crucial importance, we have combated it and have found that the repeated administration of bicarbonate during the first three to four days of the poisoning is very effective. As methanol is eliminated from the body very slowly, acidosis is very liable to recur. The amount of bicarbonate to be given is calculated according to *van Slyke's* nomogram. When there are no facilities for measuring the alkali reserve, the administration of bicarbonate should be continued till the urine gives a faintly alkaline reaction.

When treatment is carried out correctly, both life and vision can with absolute certainty be saved provided treatment is instituted before severe acidosis has set in. Patients with severe acidosis and slight or moderate reduction of vision will also always recover normal vision. Great diminution of vision may be completely repaired if it has not lasted long; otherwise normal vision will not be regained.

The great differences in the effects of methanol on various persons have always been traced to great differences in personal predisposition. This notion is not confirmed by my investigations. Many of my patients had also drunk ethyl alcohol which I have found to act as a powerful antidote, as shown by certain illustrative cases (tables 1–3).

Patient No. 3 drank about 100 ml of a liquid which on chemical

Table 1

Case No.	Methanol ml	Ethyl alcohol ml			Symptoms			Result
		1st day	2nd day	3rd day	2nd day	3rd day	4th day	
3	$<\times$	—	—	—	+	+	+++	Amblyopia
4	$\times$	98	—	—	—	+++	—	Death 3rd day
L. K.	$>\times$	98	45	32	—	—	—	Sympt.-free
E. H.	$\times$	98	45	32	—	—	—	Sympt.-free

analysis was found to contain 62% methanol by weight, i.e. about 78 ml methanol. The two last patients—L. K. and E. H.—who drank ethyl alcohol both before and after the poisoning, showed no signs of it and were not admitted to hospital. Patient No. 4 showed signs of poisoning much later than patient No. 3, and the former's prolonged latent period must be traced to the ethyl alcohol which he consumed just before he was poisoned by methanol. The fact that this patient, in spite of the prolonged latent period, developed more severe signs of poisoning than patient No. 3, may be explained by his having drunk more methanol.

The varying course of the poisoning in the next three cases is indicated in table 2.

Table 2

Case No.	Methanol ml	Ethyl alcohol ml.		Symptoms 3rd day	Alk. res. vols.% 4th day	Result and remarks
		2nd day	3rd day			
16	×	—	—	+++	15	Amblyopia
17	×	—	168	+++	27	Normal vision
O. H.	×	>158	168	—	—	Drunk 4th day No symptoms

It will be seen that the patient O. H., who drank large quantities of ethyl alcohol on several days in succession, showed no signs of poisoning and was not admitted to hospital. Patient No. 16 showed signs of severe acidosis on the third day and was practically blind. Patient No. 17, who consumed large quantities of ethyl alcohol after he had developed signs of severe poisoning (vomiting, pain in back and limbs, diminution of vision) made a rapid recovery and possessed practically normal vision on admission to hospital.

Lastly, I would refer to three patients who, it was stated, consumed the same quantity of methanol, and whose blood contained approximately the same quantity of volatile reducing substance (calculated as methanol).

Table 3

Case No.	Methanol ml	Ethyl alcohol ml. 1st day	Volat. red. s. in blood % 2nd day	Alk. res. vols.% 2nd day	Treatment and result
22	233	—	0.161	—	Not treated. Death 2 hours later.
23	233	—	0.183	25	Bicarb. intraven. Normal vision.
24	233	74	0.181	34	Bicarb. Normal vision.

Patient No. 24 drank ethyl alcohol some three hours before he consumed methanol with his companions. About 9 ml of ethyl alcohol are eliminated hourly from the body. Therefore barely 50 ml of ethyl alcohol can have been present in the body when he was poisoned. This patient was admitted to hospital 3 ½ hours later than patient No. 23 and suffered, in opposition to this patient, from a moderate degree of acidosis only. The comparatively small quantity of ethyl alcohol which he had consumed had thus delayed the development of acidosis in spite of the concentration of methanol in the blood being high. Whereas patient No. 23 had greatly reduced vision on recovering consciousness after the first treatment, and did not recover normal vision until a week later, the vision of patient No. 24 was normal on his admission to hospital. He was fetched by the police and admitted to hospital because it was learnt that he had consumed methanol with the two other patients.

Investigations have always shown that when no ethyl alcohol has been consumed with methanol, the poisoning runs the most acute course in those who have consumed most methanol. This would hardly have been the case, were personal predisposition to play any important part.

How can we then explain the curious facts that patients always become blind before they die, and that severe acidosis is an essential condition for the development of amblyopia and amaurosis?

The marked effect of methanol poisoning on the retina can best be explained by assuming the existence of a chemical combination of formic acid with the iron in the respiratory ferment; for the retina, according to the investigations of *Otto Warburg*, is in greater need of oxygen in relation to its iron content than any other tissue.

The concentration of formic acid in the blood was investigated in 8 cases in which it ranged from 3 to 19 mg%, but its concentration was not proportional to the severity of the clinical picture. Thus a patient with a concentration of formic acid in the blood of 5,7 mg% was moribund, while another patient with a concentration of 7,2 mg% and with signs of severe poisoning and marked amblyopia recovered. The alkali reserve in these two cases was 8 and 15 vols.% respectively.

If we now assume that the reaction between the formic acid and the respiratory ferment depends on the concentration of hydrogen ions in such way that the amount of formic acid tied to the ferment rises with the rise of the hydrogen ion concentration, an explanation is given for the great susceptibility of the retina and for the important part played by acidosis.

If formic acid is the primary factor determining the development of methanol poisoning, the antitoxic effect of ethyl alcohol becomes plain.

Because its surface activity is greater than that of methanol, the latter will be displaced from the respiratory ferment, and the oxydation of methanol to formic acid will thereby be prevented.

Table 4

Alkali Reserve in Rats after Poisoning with 8 ml. Methanol per kg Body Weight

Rat's No.	Weight in g	Alkali Reserve vol.%	
		2nd day	3rd day
13	350	49	—
14	450	55	—
15	420	59	—
16	440	60	—
17	290	56	—
18	390	—	47
19	480	—	55
20	370	—	49
21	270	—	53

Table 5

Methanol Poisoning in Rabbits

Rabbit's No.	Weight in kg	Day of test	Ml methanol per kg body weight	Alk. res. vol. %	Reaction of pupils	Remarks
1	1	1	4	54		*7th day, hr. 22:*
		2	3	49	++	Rabbit moribund.
		3	5	45	++	Pupils not react-
		4	4	47	++	ing to light.
		5	5	53	++	Alk. res. 79 vol.%.
		7	7	67	++	
2	1.4	1	7	59		*2nd day's evening:*
		2	7	46	++	Comatose. Pupils
		3	5	48	+	not reacting to light.
3	1.25	1	8	58		
		2	—	38	+	
		3	—	67	++	
4	1.6	1	10	—		Coma. 2nd day:
		2	—	54	÷	Moribund. Killed.
5	2.4	1	8	—		
		2	—	44	++	
		3	—	—	++	

++: Pupil reaction normal.
+: Pupil reaction weak.

The inability of *Haskell* and his associates to demonstrate severe acidosis in dogs poisoned with methanol has already been referred to. I have myself been unable to demonstrate any appreciable reduction of the alkali reserve in rats and rabbits (tables 4 and 5).

By histological examinations I have succeeded in demonstrating great degenerative changes in the retinæ's ganglion cells of human beings who had died of methanol poisoning. The nuclei were situated in the extreme periphery of the cells, being angular and pressed flat, and with the nucleolus in the periphery. There was central tigrolysis with remains of tigroid substance in the periphery.

I have not succeeded in demonstrating any similar changes in the retinæ of rats and rabbits. This fact, in association with the absence of severe acidosis in experimental animals, shows that there is a fundamental difference between the action of methanol on man and experimental animals. Experiments on the latter are undoubtedly to blame for the impression that acidosis plays no part of importance in the course run by methanol poisoning. This impression has contributed to the neglect of the treatment of acidosis and to the loss of life or vision of many human beings.

Summary

Clinical investigations of methanol (methyl alcohol) poisoning in Norway have shown that the outcome of poisoning depends entirely on the degree of acidosis. Ethyl alcohol acts as a powerful antidote. By post-mortem examinations very pronounced degenerative changes are found in retinæ's ganglion cells.

The author has not found similar changes in the retina of experimental animals, who do not develop a marked acidosis. There are thus fundamental differences in the action of methanol on human beings and on animals.

Zusammenfassung

Klinische Untersuchungen über Methanol(Methyl-Alkohol)-Vergiftung in Norwegen haben gezeigt, daß die Vergiftungsfolgen völlig vom Grad der Acidose abhängen. Äthylalkohol ist ein kräftiges Antidot. Bei der Sektion wurden sehr starke degenerative Veränderungen in den Ganglienzellen der Retina gefunden.

Der Autor fand keine ähnlichen Veränderungen in der Retina von solchen Versuchstieren, welche keine deutliche Acidose entwickelten. Es bestehen fundamentale Unterschiede hinsichtlich der Wirkung von Methanol bei Mensch und Tier.

Résumé

Des recherches cliniques sur l'intoxication par le méthanol (alcool méthylique) en Norvège montrent que les conséquences de l'intoxication sont entièrement dépendantes du degré d'acidose. L'alcool éthylique agit comme un antidote puissant. Les résultats d'autopsies révèlent des lésions dégénératives profondes dans les cellules ganglionnaires rétiniennes.

L'auteur n'a pas trouvé de lésions analogues dans la rétine des animaux d'expérience qui ne présentent pas d'acidose marquée. Il y a donc des différences fondamentales dans l'effet du méthanol chez l'homme et chez l'animal.

Riassunto

Ricerche cliniche sull'avvelenamento coll'alcool metilico (metanolo) in Norvegia, hanno mostrato che le conseguenze dell'avvelenamento dipendono assolutamente dal grado dell'acidosi. L'alcool etilico è un forte antidoto. L'autopsia ha rivelato importanti modificazioni degenerative delle cellule ganglionari della retina.

Non è riuscito all'autore di determinare modificazioni simili nella retina degli animali, che non presentavano un'acidosi marcata. Esistono differenze fondamentali tra l'azione dell'alcool metilico nell'uomo e nell'animale.

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