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Severe Methanol Intoxication

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Haemodialysis or peritoneal dialysis has since 1960 been used in a few cases of methanol poisoning in man for the purpose of hastening the elimination of methanol. This form of therapy has been recommended as a supplement to the current treatment with ethyl alcohol and alkali (2, 17, 49, 51, 54).

In 1961, 4 patients with methanol poisoning were transferred to this clinic; all had severe acidosis, and were stuporous or comatose at or shortly after admission to a previous hospital. They were treated by haemodialysis (in the Addendum are mentioned 2 patients who were later treated by haemodialysis) and with ethyl alcohol and sodium-bicarbonate. The elimination of methanol and its metabolite, formic acid, was checked by analysis of serum, urine and dialysing fluid. Three of the 4 original patients needed artificial respiration. These 3 died in the acute phase of the disease; the fourth patient recovered but died from another disease 1 1/2 years later. Autopsy was performed in all four cases.

Methods

The dialyses were carried out with Alwall's (3, 4) type of artificial kidney. The blood flowed through the machine at a rate of 150—300 ml/min. The dialysing fluid contained 120 mEq of sodium, 4.9—5.8 mEq of potassium, 2.8 mEq of calcium, 0.8 mEq of magnesium, 100 mEq of chloride, 35 mEq of bicarbonate, and 10 g of glucose per litre. It was aerated continously with about 5 litres of carbogen (95 % oxygen plus 5 % carbon dioxide) per minute.

The concentration of methanol in serum, urine, and dialysing fluid was determined by Feldstein and Klendshøj's micro-diffusion method (16). In all the samples the methanol concentration was determined in the acute phase and was also checked by subsequent analyses. An improved modification of the method has recently been published by Hindberg and Wieth (25) and was used in the cases mentioned in the Addendum.

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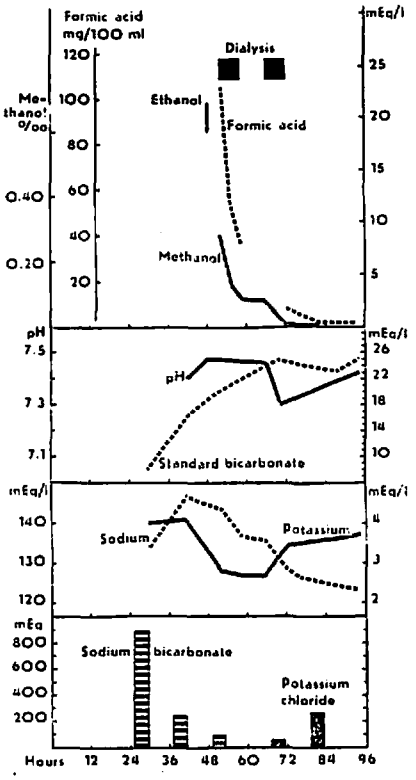

Fig. 1. Case 1. Serum levels of methanol, formic acid, sodium, and potassium; variations in pH and standard bicarbonate in capillary blood; administered amounts of sodium bicarbonate and potassium chloride per 12 hours. The arrow indicates the time at which administration of ethanol was started. The square indicates the duration of dialysis.

All the serum and urine samples were also tested for formaldehyde by Feldstein and Klendshøj's technique (16). The content of formic acid was determined by the method described by Bastrup (8). Standard bicarbonate, pH, and pCO_2 in capillary blood were determined by Sigaard-Andersen's et al. micro-technique. (50).

The patients were among 30 cases of methanol poisoning that occurred in 1961 in South Sweden. A number of bottles containing 100 % methanol for technical use were sold as ethyl alcohol. A preliminary report of the four cases treated by us has been published (32).

The times given in the report refer to the number of hours after the first intake of methanol.

Case reports

Case 1. A 49-year-old stevedore who had earlier been in good health and, according to information, was not an alcohol addict. At a drinking party he consumed an unknown amount of methanol. After 15 hours he experienced failing vision. After 24 hours he had abdominal pain, vomiting, giddiness, disturbances of hearing, and deep respiration. He was admitted to hospital after 28 hours, with clouding of consciousness and motor restlessness. The pupils were dilated and no vision could be demonstrated. Standard bicarbonate was 8 mEq/l. Soon after admission the degree of wakefulness diminished further and he passed into coma after 29 hours. Infusion of sodium-bicarbonate was started and continued up to the first dialysis treatment. Because of falling blood-pressure, down to 70 mm Hg, treatment with metaraminol (Aramine®) was instituted. Tracheotomy was performed after 36 hours.

On admission to this clinic after 48 hours he was in coma; cutaneous oedema and papillary oedema were noted. The eyelid-closure reflex and weak pupillary reflexes were present but reaction to pain was absent. The WBC was 12,800/mm³ and he had neutrophilia. Tests with Albustix® and Clinistix® showed proteinuria and glycosuria, and the sediment contained large amounts of red blood cells. The urine was acid. The ESR was 12 mm in an hour.

During infusion of sodium-bicarbonate pH was 7.48, standard bicarbonate 19.2 mEq/l and pCO_2 21.5 mm Hg. At admission to this clinic administration of ethyl alcohol was also started.

After 52 hours a 6-hour dialysis was begun; infusion of ethyl alcohol and sodium-bi-

TABLE I. Effect of first haemodialysis in each patient. In cases 3 and 4 the dialysing fluid was changed in the middle of the treatment

Case	Weight (kg)	Duration (hrs)	Serum concentration: Methanol (‰) Before dialysis	Serum concentration: Methanol (‰) After dialysis	Serum concentration: Formic acid (mg/100 ml) Before dialysis	Serum concentration: Formic acid (mg/100 ml) After dialysis	Concentration in dialysing fluid (140 l): Methanol (‰)	Concentration in dialysing fluid (140 l): Formic acid (mg/100 ml)	Total amounts removed: Methanol (g)	Total amounts removed: Formic acid (g)
1	92	6	0.275	0.092	104.7	36.8	0.048	11.9	6.7	16.7
2	70	6	0.277	0.072	68.0	28.8	0.039	10.1	5.5	14.1
3	55	4	0.860	0.570	37.8	11.9	0.088	2.0	12.3	2.8
		4		0.500			0.040	1.0	5.6	1.4
4	63	4	0.194	0.078		9.5	0.016	7.3	3.3	10.3
		4		0.063		2.2	0.012	1.5	1.7	2.1

carbonate was continued during the dialysis treatment. By that time a total of 1200 mEq of sodium-bicarbonate had been infused. The potassium concentration in serum, which before the dialysis treatment was 2.8 mEq/l did not rise despite a high content of potassium in the dialysing fluid. The concentrations of methanol and formic acid are shown in fig. 1 and table I.

Respiratory insufficiency necessitated artificial respiration after 55 hours. A second dialysis was begun after 66 hours. Despite intravenous administration of 65 mEq of potassium-chloride and dialysis against potassium-rich fluid, the serum-potassium level rose from 2.7 to only 3.4 mEq/l. At the end of the second dialysis the concentrations of methanol and formic acid were very low. The patient's condition was unchanged: he was in deep coma and had a tendency to a fall in blood-pressure. After infusion of another 270 mEq of potassium-chloride intravenously during the next 17 hours, serum-potassium rose to 3.9 mEq/l. Urinary output, 200—900 ml per day, ceased almost completely after 120 hours. Large amounts of metaraminol were given, up to 1100 mg/24 hours, to maintain the blood-pressure above 80 mm Hg. The patient died after 136 hours.

Post mortem examination (4 hours after death): The brain, which weighed 1,550 g, was strikingly soft with pressure grooves on the uncus gyri hippocampi and the cerebellar tonsils. The convolutions of the brain were flattened. The leptomeninges showed greyish-red discolouration around large vessels. Basally in the subarachnoidal space there was a moderate amount of blood. In both cerebral hemispheres were large haemorrhages (fig. 2), on the right side within the putamen, pallidum, and the internal capsule and on the left side mainly in the lateral part of the putamen and the surrounding area. The haemorrhages had broken through into the ventricular system in several places and through the torn floor of the third ventricle into the subarachnoid space. The left pallidum and the thalamus were flattened and deformed. The preserved parts of the putamen and the head of the left caudate nucleus were dark greyish-red. The rest of the brain substance showed diffuse dirty pale-greyish

Fig. 2. Case 1. Large haemorrhages in both hemispheres.

discolouration. No thrombi were seen in the sinuses and the basal arteries. The lungs showed marked oedema and the bronchi contained profuse viscid turbid secretion. The liver showed diffuse fatty degeneration. The kidneys weighed together 450 g; their surfaces were smooth and pale, and the cut surfaces were pale with indistinct markings in the cortical marrow.

Microscopical examination: There was a massive necrosis of the brain with distinct degenerative changes of the ganglion cells everywhere in the brain, such as simple shrinkage, severe cell degeneration (Nissl's "schwere Zellerkrankung"), ischaemic cell degeneration, karyolysis, and disappearance of the cells. Even the glia cells were degenerated, with pycnotic nuclei, karyorrhexis, and karyolysis. Nowhere were any signs seen of neuronophagia or satellitosis. No fatty-granule cells were seen. The vessel walls were well preserved without perivascular infiltrates. The cerbellum was strikingly changed, with total necrosis of the stratum granulosum, loss of nuclei in Bergmann's glia and most of Purkinje's cells. The remaining Purkinje's cells showed all degrees of degeneration. In the connective tissue around the optical nerve were polymorphonuclear leucocytes, both discrete and in aggregates. Staining of the myelin sheath of the optic nerve showed no degernerative changes. The connective tissue round the hypophysis also showed infiltrates of leucocytes. Nissl's substance in the ganglion cells of the eyes was not demonstrated (staining according to Einarsson's gallocyanin method).

The proximal renal tubules showed varying degree of necrosis with partial shedding of the epithelial cells and the lumina contained numerous granulated cylinders. The glomeruli were unchanged.

The liver had undergone generalised fatty degeneration without increase of the periportal connective tissue or of inflammation.

Methanol and formaldehyde could not be demonstrated in the blood, liver, or kidneys.

Case 2. A 65-year-old stevedore had been operated on for duodenal ulcer but had otherwise been in good health. He was an alcohol addict and took part in the same drinking-bout as case 1. He consumed an unknown amount of methanol. After 15 hours he had nausea, vomiting and headache and after 19 hours failing eye-sight. After 30 hours he was admitted to hospital. He had deep respiration and slight cyanosis of the lips and ears. The pupils were dilated but reacted to light and convergence. He was colour-blind and had visual acuity of about 0.3. The WBC was 16,500/mm³. Standard bicarbonate in serum, 11 mEq/l, fell despite administration of sodium-bicarbonate orally and by infusion to 8 mEq/l after 42 hours. Gradually developing coma and respiratory insufficiency necessitated tracheotomy and respirator treatment.

After 48 hours he was transferred to this clinic. By then he was in deep coma, had loss of reflexes, and feeble spontaneous respiration. Cutaneous oedema and papillary oedema were noted. Falling blood-pressure necessitated treatment with metaraminol, which

during the subsequent course had to be given continuously. The WBC was 7,100/mm³, 85 % being neutrophils. Proteinuria and glycosuria were diagnosed with Albustix® and Clinistix®, the sediment contained a large number of red blood cells. The diastase content in the urine was normal. Blood-pH was 7.45, standard bicarbonate 20.0 mEq/l and pCO_2 25.5 mm Hg after a total of 1,500 mEq of sodium-bicarbonate had been given (fig. 3).

Treatment with ethyl alcohol was started after 48 hours. Dialysis was begun after 53 hours. During the first few hours of the dialysis the amounts of ethyl alcohol given were only slightly increased. After 55 hours the concentration of ethyl alcohol in the blood was 0.2 ‰. During the next hour the administered amount was increased to 60 g. The level in the blood rose to 1.1 ‰. During the remaining 3 hours of dialysis he was given 94 g of ethyl alcohol, and the concentration in the blood rose to 2.0 ‰. 14 g of ethyl alcohol were found in the dialysing fluid for this 3-hour period. A second dialysis was begun after 66 hours. No clinical improvement was noted. The patient had severe hypopotassaemia. the lowest value being 1.6 mEq/l, and was given a total of 160 mEq potassium-chloride by intravenous infusion. Oliguria developed within about 60 hours. The patient died within 79 hours.

Post-mortem examination (36 hours after death): The brain, which weighed 1,600 g, was soft and the leptomeninges around large vessels were dirty greyish-red. The lateral parts of the putamina were dark greyish-red, the medial parts were paler. The rest of the brain substance was pale and dirty greyish-red. In the upper part of the pons were numerous small to cherry-stone-sized partly confluent, haemorrhages not extending into the ventricular system.

The lungs were oedematous with areas of atelectasis and showed acute bronchitis. The liver had undergone marked generalized fatty degeneration. The kidneys, weighing together 300 g, were slightly pale; the cortex of the cut surface was somewhat paler than the marrow.

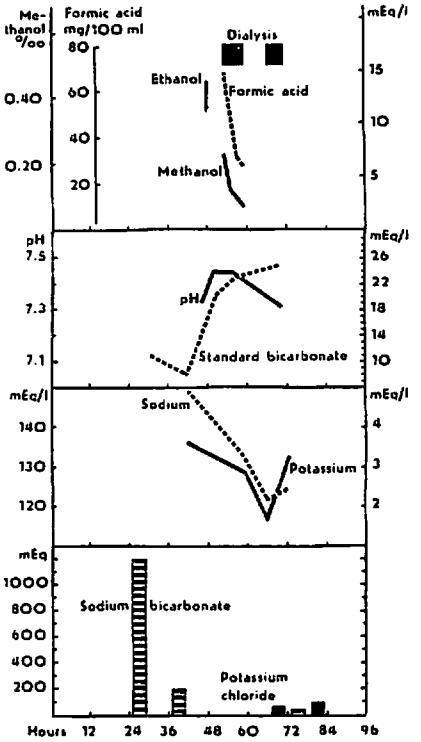

Fig. 3. Case 2. Serum levels of methanol, formic acid, sodium and potassium: variations in pH and standard bicarbonate in capillary blood; administered amounts of sodium-bicarbonate and potassium-chloride per 12 hours. The arrow indicates the time at which administration of ethanol was started. The square indicates the duration of dialysis.

Microscopical examination: The brain showed virtually the same changes as in case 1. Ganglion and glia cells exhibited all stages of degeneration without signs of reaction. In the putamina were numerous small perivascular haemorrhages. The cerebellum showed necrosis of the stratum granulosum with loss of Bergmann's glia and some Purkinje's cells.

There were no inflammatory infiltrates around the optical nerve. Nissl's substance in the ganglion cells of the eye could not be demonstrated (staining according to Einarsson's gallocyanin method).

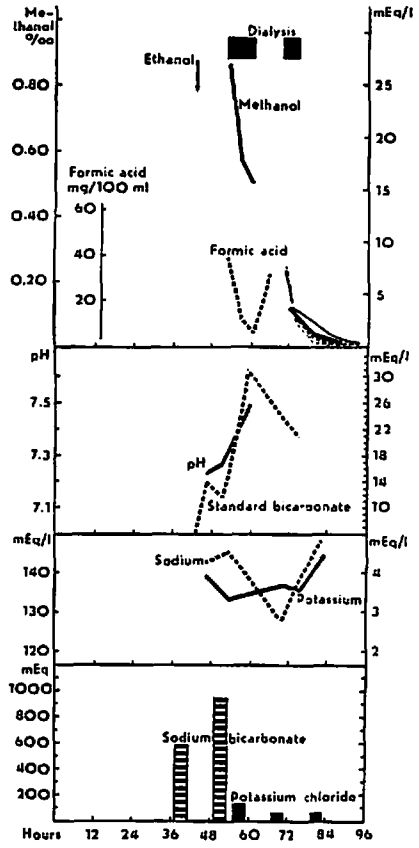

Fig. 4. Case 3. Concentration of methanol and formic acid in serum and urine; serum levels of sodium and potassium; variations in pH and standard bicarbonate in capillary blood; administered amounts of sodium bicarbonate and potassium chloride per 12 hours. The thick lines represent the serum levels and the thin lines the urinary levels. The arrow indicates the time at which administration of ethyl alcohol was started. The square indicates the duration of dialysis.

The kidneys showed the same changes as in case 1. Evaluation of the changes was difficult owing to autolysis. Methanol, 0.27 ‰, was found in the brain but there was none in the blood, liver, and kidneys. Formaldehyde was not found in the examined organs.

Case 3. A 49-year-old waitress who was known to be an alcohol addict drank about 40 g of methanol and 29 hours later another 50 g at least. After 40 hours she left work and after 42 hours she was found sitting unconscious at home. At hospital, immediately afterwards, deep respiration was noted. After 43 hours respiratory standstill occurred and she had a blood-pressure fall with impalpable peripheral pulse. In response to intubation, manual respiration, and infusion of sodium-bicarbonate with ethyl alcohol and metaraminol, circulation became satisfactory.

At her admission to this clinic after 44 hours tracheotomy was performed and respirator treatment was started. By then she was in coma and had slight peripheral cyanosis. The pupils were of normal size and reacted to light. Reaction to pain and tendon reflexes were absent. The WBC was 17,800/mm³. Urine tests with Albustix® and Clinistix® were positive and the sediment contained large numbers of red cells. The diastase content in the urine was normal.

Blood-pH was 7.24, standard bicarbonate 14.1 mEq/l, and pCO_2 30.0 mm Hg after infusion of a total of 600 mEq of sodium-bicarbonate (fig. 4).

Dialysis treatment was started after 53 hours. After 5 hours of dialysis, with continued sodium-bicarbonate infusion, pH was 7.49, standard bicarbonate 31 mEq/l, and pCO_2 44.0 mm Hg. A total of 1600 mEq sodium-bicarbonate by infusion had then been given. During dialysis, 130 mEq of potassium-chloride were infused and serum-potassium rose from 3.3 to 3.6 mEq/l. At the end of the treatment the pupils were dilated and without reaction to light. Slight papillary oedema was noted. A second dialysis was begun after 70 hours. The patient was still comatose. Metaraminol, up to 1100 mg/24 hours, was given to maintain the circulation. Because of suspected oedema of the brain, urea was administered intravenously. The depth of coma remained unchanged, however. Initially, she had polyuria of up to 7 litres of urine per day, but oliguria developed within about 100 hours. The patient died in circulatory failure within 110 hours.

Post-mortem examination (4 hours after death): The brain, which weighed 1,600 g, was strikingly soft and showed pale dirty greyish-red discolouration. In the left cerebral hemisphere there was a large haemorrhage which involved the putamen and the surrounding area and had broken into the anterior horn of the lateral ventricle (fig. 5). The whole of the right putamen showed a marked dirty greyish-red discolouration. The ventricular system was filled with blood which, via the normal foramina, had entered between the soft membranes on the base of the cerebrum.

Pulmonary oedema and tracheobronchitis were present. The kidneys showed the same gross and microscopical changes as in case 1.

Microscopical examination: The histological examination showed the same changes in the brain as in the two previous cases, but in this case there was massive necrosis without reactions of the glia and vessels. Nissl's substance in the ganglion cells of the eye could not be demonstrated. No methanol or formaldehyde were found in blood, liver or kidneys.

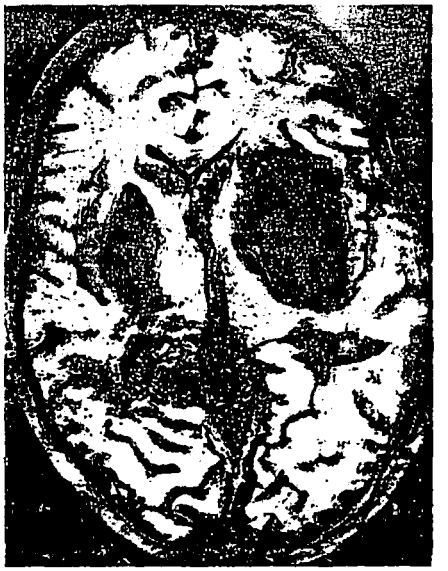

Fig. 5. Case 3. A large haemorrhage in the left hemisphere. The ventricular system is filled with blood.

Case 4. A 39-year-old house-wife who was addicted to ethyl alcohol had for some years had a cough and wheezing respiration. She drank about 80 g of methanol. After 9 hours she began to have violent vomiting and a few hours later she experienced an ache, first in the back and then diffusely all over her body. After 36 hours she noticed failing eye-sight. On admission to hospital after 44 hours she was blind and had deep respiration. She complained of sensory disturbances in the legs. Infusion of sodium-bicarbonate and ethyl alcohol was started.

On arrival to this clinic after 45 hours she had clouding of consciousness. She answered when spoken to but her speech was slurred and she was disoriented as to time and place. She was not able to distinguish between light and darkness but her pupils reacted to light. She had deep respiration and sounds as caused by secretion were heard over both lung-fields. Despite continuous infusion of sodium-bicarbonate, pH was 7.09, standard bicarbonate 8.3 mEq/l, and pCO_2 17.0 mm Hg. Serum-potassium was 3.3 mEq/l (fig. 6). The urine was acid; test with Albustix® was positive and with Clinistix® negative. The diastase content in the urine was 512 units (Wohlgemut). The sediment contained large numbers of red and white blood-cells. WBC was 17,100/ mm^3, 91 % of which were neutrophils. The ESR was 102 mm in an hour. The patient had a temperature of 39° C. Stagnation of bronchial secretion necessitated tracheotomy.

Dialysis treatment was started after 50 hours. The patient was then comatose and did not react to pain. She had satisfactory spontaneous respiration. Circulation was maintained with small amounts of metaraminol. During dialysis the patient awoke and vision returned. At the completion of dialysis, within 58 hours, she responded adequately when spoken to and could read ordinary newspaper print. By then she had received a total of 1,300 mEq of sodium-bicarbonate by continuous infusion and pH was 7.58, standard bicarbonate 32 mEq/l, and pCO_2 33 mm

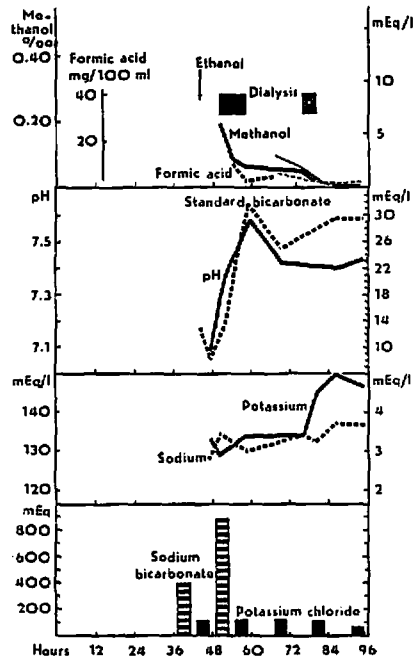

Fig. 6. Case 4. Concentration of methanol and formic acid in serum and urine; serum levels of sodium and potassium; variations in pH and standard bicarbonate in capillary blood; administered amount of sodium bicarbonate and potassium chloride per 12 hours. The thick lines represent the serum levels and the thin lines the urinary levels. The arrow indicates the time at which the administration of ethyl alcohol was started. The square indicates the duration of dialysis.

Hg. Despite infusion of a total of 240 mEq of potassium-chloride since her arrival at the clinic, serum-potassium was unchanged at 3.3 mEq/l. Within 76 hours a second dialysis was started. An EEG taken after 180 hours showed some slight diffuse theta activity with asymmetrical response to flicker. Examination of the eyes after 120 hours showed no abnormalities.

The patient never called for a doctor again. According to information from her relatives, she caught a cold about 1 1/2 years after the methanol poisoning, had pain in the chest

Fig. 7. Case 4. Slit-shaped cysts in the lateral parts of both putamina.

and the back, and high fever. Her condition deteriorated and she died after a few days.

Post-mortem examination: In the brain slit-shaped cysts were seen in the lateral parts of both putamina (fig. 7). There were extensive bronchopneumonic foci, notably in the two lower lobes. In both lungs were areas of moderate bronchiectasis. The spleen exhibited the typical picture of infection. The heart was normal, without any signs of right-sided hypertrophy. Gastric ulcer and diffuse fatty degeneration of the liver were diagnosed.

Microscopical examination: Round the above-mentioned cysts was a pronounced glia proliferation. The cysts were filled with vascularized loose connective tissue and a few macrophages. The cerebellum showed in several places small sclerotic areas with loss of Purkinje's cells and stratum-granulosum cells as well as proliferation of Bergmann's glia.

Discussion

Symptoms and course

In 3 of the 4 cases information is available about the symptoms of intoxication before admission to hospital. Two patients fell ill within 9 and 15 hours, respectively, of the intake of methanol with nausea, vomiting, and headache. One patient had failing eye-sight as the first symptom within 15 hours, the other two

experienced impaired vision within 19 and 36 hours, respectively. Deep respiration was noted in 1 patient within 24 hours. In the others this symptom was noted at admission to hospital within 30, 42, and 44 hours, respectively. By then, all had severe metabolic acidosis with standard bicarbonate between 8 and 14.1 mEq/l in 2 cases measured during the course of alkali therapy, which was started within 29, 30, 43, and 44 hours, respectively. Ethyl alcohol was instituted within 48, 48, 43, 44 hours, respectively. No data were obtained proving that the patients had drunk ethyl alcohol at the time of or after the intake of methanol. The first dialysis treatment was started within 52, 53, 53, 50 hours, respectively. All the patients developed hypopotassaemia. All had leucocytosis, neutrophilia, proteinuria, and microscopical haematuria as well. Three of the patients had glycosuria. One had a slightly raised level of urinary diastase. Coma occurred within about 29, 36, 42, and 48 hours, respectively. Artificial respiration was required because of pulmonary insufficiency in 3 cases and was started within about 55, 36, and 43 hours, respectively. Oliguria-anuria developed in these patients within about 120, 60, 100 hours, respectively, and death occurred within 136, 79, and 110 hours. The fourth patient, who survived her intoxication for 1 1/2 years, died from unrelated pneumonia, the development of which was promoted by bronchiectasis.

Post-mortem findings

The 3 patients who died as a result of their methanol intoxication had massive necrosis of the brain without reaction of the glia or the vessels. This suggests that the changes were due mainly to autolysis, which started intra vitam. It is sometimes seen after prolonged respirator treatment of deeply unconscious patients with respiratory insufficiency (11, 37). In our cases the respirator was used for 81, 43, and 66 hours, respectively. The massive necrosis of the brain made it difficult to assess the findings that may be considered to result directly from the methanol poisoning, notably the necrosis in the putamina (42). Patients nos. 1 and 3 had massive haemorrhages into the putamina and their surroundings, breaking into the lateral ventricles. The confluent haemorrhages into the pons in case 2 were probably attributable to the increased intracranial pressure. In this case the putamina were strikingly soft and of a greyish-red colour as a result of small perivascular haemorrhages, as has also been described by Orthner (42).

The inflammatory changes in the connective tissue around the optical nerve and the hypophysis with a very dense accumulation in some areas of polymorphonuclear leucocytes in case 1, were striking. Whether this inflammation is an effect of the methonal poisoning or not cannot be established. Inflammatory infiltrates in the connective tissue around the hypophysis, though not around the optical nerve, have sometimes been seen in massive necrosis of the brain in unconscious patients given respirator treatment (56).

In patient no. 4, who was not treated with artificial respiration in connection with her intoxication, autopsy showed symmetrical slit-shaped cysts in the

lateral parts of the putamina. These changes, as well as the haemorrhages into the putamina in the other cases, correspond to the pattern of injuries which according to Orthner is typical of methanol poisoning.

It cannot be established whether the small sclerotic areas in the cerebellum with loss of Purkinje's cells and stratum-granulosum cells and proliferation of Bergmann's glia cells seen in case 4 were residual changes of necrosis in association with methanol poisoning (27) or ethyl-alcohol addiction (38). Such necroses have also been seen in uraemia of various origin (41) and in disturbances of the carbohydrate metabolism — diabetic coma, insulin poisoning (12, 31, 48, 55).

Case 4 is of special interest because it is the first case in which probably residual changes of necrosis in the putamen have been demonstrated in a patient who survived a methanol intoxication.

Toxicology

The toxic effects in methanol poisoning are produced in association with the breakdown of the substance and are to some extent correlated to the severity of acidosis that develops. The metabolites of methanol — formaldehyde and formic acid — can only partly explain the development of severe acidosis (15, 43, 46, 47). It must also be due to acid radicals that form as a result of secondary metabolic disturbances (47). The formic-acid concentration can to some extent be said to be a measure of the amount of metabolised methanol. The concentrations of methanol and its metabolite formic acid in serum and urine of all our 4 patients are shown in table I and fig. 1. On their admission to this clinic, within 44—48 hours of the methanol intake, patients nos. 1 and 2 had much higher concentrations of formic acid than had patients nos. 3 and 4. This means that the first two would have had time to metabolise more methanol than the latter two, which is in agreement with the time interval between the onset of symptoms of severe acidosis and the administration of ethyl alcohol, being in cases 1 and 2 about 20 hours and in cases 3 and 4 probably only a few hours.

Varying lengths of time between the intake of methanol and the institution of treatment, as well as uncertain information regarding the consumed amounts of methanol and ethyl alcohol would explain the varying statements concerning the minimum lethal dose of methanol, 25—200 g, found in the current toxicological textbooks (5, 18, 36). Early treatment has prevented death or visual defects even after high consumption of methanol, for instance about 250 and 200 g, respectively, in Røe's cases nos. 65 and 77 (46). Untreated methanol poisoning can prove fatal, judging by Røe's series, after intake of about 100 g and lead to transient blindness after 40 g. Wieth and Jorgensen (54) described a case in which the patient had drunk about 80 g of methanol. The patient died despite adequate bicarbonate treatment started within 18 hours and haemodialysis within 30 hours of the intake. In our case 3 about 90 g led to a fatal outcome and in case 4 about 80 g caused transient blindness, coma, and persistent although not clinically manifest brain damage. In both these cases the treatment was started first

within about 43 and 44 hours, respectively. Then, one of the patients was in coma and had circulatory failure, and total blindness had developed in the other. On these grounds, the minimum lethal dose of methanol in untreated adults can be set at probably less than 80 g. A risk of visual defects will probably attend the consumption of half this amount, which means an initial serum-methanol concentration of about 1 ‰ at a body-weight of 70 kg. At a lower serum-methanol concentration a severe acidosis as evidence of advanced methanol oxidation may signify that the risk of visual defects and death is imminent. This is illustrated by our four cases in which the concentrations of methanol in serum were low at the beginning of the treatment.

Treatment

It may be considered established that ethyl alcohol inhibits the breakdown of methanol in man and the rhesus monkey (21, 30). According to Bartlett's (7) studies with C^{14}-labelled methanol, an ethyl-alcohol concentration in serum of 0.46 ‰ inhibits the metabolism of methanol to 70 %. Clinical experience indicates that an ethyl-alcohol concentration in the blood of 1 ‰ causes virtually total inhibition of the methanol oxidation (1, 46). The reason why the clinical value of ethyl-alcohol treatment in methanol poisoning (46) earlier has been questioned (35 a. o.) would be results of animal experiments with non-primates (19, 34) whose methanol metabolism, according to later studies, is not the same as that of man (20).

Our patients were given ethyl alcohol according to the principle devised by Roe (46). The breakdown of methanol seems to have been virtually completely inhibited in cases 1, 2, and 4. In case 3, on the other hand, the methanol concentration fell and the formic-acid concentration rose between the two dialysis treatments, as will be seen from fig. 4. The patient had, reasonably, not received sufficient compensation for the increased elimination of ethyl alcohol during the dialysis. The figures quoted in the early literature for the rate of breakdown of ethyl alcohol are probably too low. According to later experience (13), the rate of breakdown of ethyl alcohol in a normal person amounts to 10—12 g per hour. The amount of ethyl alcohol removed by dialysis during the treatments had to be replaced by extra administration. There are no earlier experiences with the ethyl-alcohol clearance of our dialysing machine and, as will be seen from the case-reports, especially case 2, it was difficult to estimate the suitable dose of ethyl-alcohol administration during dialysis treatment. Samples for determination of ethyl alcohol were taken at the first dialysis in case 2. Ninety-four grammes of ethyl alcohol were given during the last three hours of dialysis. The patient would break down approximately 30 g in that time. Fourteen grammes were recovered from the dialysing fluid. The remaining 50 g increased the concentration in the blood from 1.1 ‰ to 2.0 ‰. To avoid the difficulties of intravenous administration of ethyl alcohol during dialysis it would be possible to use a dialysing fluid with an ethyl-alcohol concentration of 1 ‰.

Treatment with alkali in methanol poisoning attended with acidosis has long been practised (24, 26). Clinical experience and experimental studies in monkeys (9, 10, 44, 54) have shown that visual defects and death cannot always be prevented in methanol poisoning if treatment consists only of correction of acidosis with alkali. Probably, the duration of acidosis plays an important role. Our findings are not inconsistent with the view that adequate treatment with bicarbonate started at an early stage reduces the risks of toxic effects. By intensive alkali treatment the pH of the blood can be corrected quickly. A change in intracellular pH is probably corrected much more slowly (14, 45, 53). In our cases 1 and 2, in which alkali was given initially, the patients deteriorated gradually although their extracellular acidosis had been corrected with 1200 and 1500 mEq of sodium-bicarbonate, respectively, orally and intravenously. The relatively large doses of sodium-bicarbonate which must be given over a short time to control an acidosis due to methanol, can produce an increase in the intracranial pressure, convulsions, and signs of pulmonary oedema (9, 46, 52), especially in the presence of renal insuffiency. In such cases in particular, dialysis is a safer method for correction of acidosis than is treatment with alkali alone. By dialysis treatment, accumulated acid radicals can be eliminated and bicarbonate administered without risk of electrolyte-fluid retention.

Because of the pronounced hypopotassaemia in our cases we gave large amounts of potassium salts intravenously, and a high-potassium dialysing fluid was used. Hypopotassaemia in methanol poisoning has earlier been observed (52). Formate formed intracellularly and possibly other anions may in these cases lead to an increased immigration of potassium ions into the cells.

Our experiences with haemodialysis are consistent with those of others (6, 17, 49, 54) in showing that the time of elimination of methanol is greatly reduced with this method. Similar results have been obtained by peritoneal dialysis (2, 51). Through the natural channels the elimination of methanol and formic acid is slow (fig. 6). Table 1 shows the elimination of methanol and formic acid during the first dialysis in each patient. In case 3 the amount eliminated over the first three days in hospital was only 7 g, in a total of 15 litres of urine, whereas 18 g were removed during the first eight-hour dialysis. The explanation of this, as will also be seen from fig. 4, is that the concentrations of methanol and formic acid in the urine are of the same order as those in serum and the rest of the body fluids. Forced diuresis which, for instance in barbiturate poisoning, greatly reduces the time of elimination of the poison (39, 40), has therefore a relatively insignificant effect on the elimination of methanol.

Post-mortem examination of the blood, liver, and kidneys revealed no methanol whereas brain tissue examined chemically in case 2 only, was found to contain 0.27 ‰ methanol. The explanation of this finding in the brain is probably interference with the circulation of blood caused by the necrosis of the brain. The intracerebral haemorrhages which have been demonstrated in cases of methanol-

induced brain lesions, may have been accentuated by heparinisation during haemodialysis. Some form of regional heparinisation is desirable (23, 29, 33 a. o.), in order as far as possible to cut down the prolongation of the clotting-time.

On the basis of others' (2, 21, 22, 28, 46, 54 etc.) and our own experiences, it seems that the main principles in the treatment of methanol poisoning should be:

1) Prompt oral or intravenous administration of ethyl alcohol in order to inhibit the methanol oxidation; about 50 g should be given initially to a 70 kg patient and thereafter about 10—12 g per hour so as to maintain an ethyl-alcohol concentration in the blood of about 1 ‰. This treatment should be continued until virtually all methanol has been eliminated.
2) Careful clinical and laboratory supervision of the patient, including, for instance, a quick method for determination of methanol and frequent checking of pH and standard bicarbonate. In patients with acidosis the serum-electrolytes, the serum-potassium content in particular, should be checked.
3) Administration of alkali in cases with acidosis. Care must be taken in severe acidosis, as the amounts of sodium-bicarbonate required for correction may involve the risk of oedema of the lungs and brain, especially if renal insuffiency is present.
4) Haemodialysis or peritoneal dialysis to ensure quick elimination of methanol and accumulated acid radicals. The indication for dialysis is strengthened in patients with impaired renal function or acute renal insufficiency as complications of methanol poisoning.
5) Tracheotomy and respirator treatment in cases of impending pulmonary insufficiency.

Summary

Four cases of methanol poisoning were treated with alkali, ethyl alcohol, and the artificial kidney. In 3 cases respirator treatment was also required. The concentrations of methanol and its metabolite formic acid in blood, urine, and dialysing fluid were checked.

Severe acidosis, failing eye-sight, and cerebral damage were present at the start of the treatment within 29 to 44 hours of the intake of methanol. Three patients, one of whom had consumed 90 g, died despite correction of the acidosis and elimination of methanol. Autopsy in these cases showed massive necrosis of the brain and haemorrhages into the putamina. The fourth patient, who had consumed 80 g of methanol, survived but died 1 1/2 years later from pneumonia; autopsy showed slit-shaped cysts in the lateral parts of the putamina. All the patients had considerable hypopotassaemia.

By haemodialysis the time of elimination was greatly reduced for methanol as well as for formic acid.

The most important procedures in the treatment of methanol poisoning should be careful clinical and laboratory supervision of the patient, inhibition of the methanol oxidation with ethyl alcohol and administration of alkali to patients

with acidosis. By dialysis treatment the time of elimination of methanol can be greatly reduced and acidosis can be effectively corrected.

Addendum

Five patients were later observed in this clinic after consumption of 300—500 ml of spirits intended for technical use. These can contain a small percentage of methanol, among other impurities. 2.5 g of methanol per 100 ml were demonstrated in the kind of spirit consumed by one of these patients. At ingestion of such spirit the amount of methanol, which is inconsiderable in relation to the quantity of ethyl alcohol, is usually of no clinical significance.

Two of these patients were treated with the artificial kidney:

1. S. L. (male, 32 years of age) had drunk 500 ml of methylated spirit. He had abdominal pain and a history of previous pancreatitis. During a 6-hour dialysis, 5 g methanol were eliminated with the dialysing fluid. The concentration of methanol in serum was reduced from 0.24 to 0.14 ‰.
2. K.J. (male, 27 years of age) had consumed 400 ml of methylated spirit. His methanol concentration in serum was inconsiderable, whereas the ethyl-alcohol concentration was 4.1 ‰, which was not known at the crucial moment in the acute phase. He had visual disturbances and urinary-bladder paresis but no acidosis. Alkali had been given at the admitting hospital.

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