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Methanol outbreak in Norway 2002–2004: epidemiology, clinical features and prognostic signs

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Abstract. Hovda KE, Hunderi OH, Tafjord A-B, Dunlop O, Rudberg N, Jacobsen D (Ullevaal University Hospital, Oslo; Ostfold Hospital Trust, Fredrikstad; and Alesund Hospital, Alesund; Norway). Methanol outbreak in Norway 2002–2004: epidemiology, clinical features and prognostic signs. *J Intern Med* 2005; **258:** 181–190.

Objectives. Knowledge on methanol poisoning does mainly come from clinical studies. We therefore report epidemiological, clinical and prognostic features from the large methanol outbreak in Norway in 2002–2004 where the new antidote fomepizole was the primary antidote in use.

Design and subjects. Combined prospective and retrospective case series study of 51 hospitalized patients who were confirmed poisoned with methanol, of whom nine died. In addition, eight patients died outside hospital. Most patients were admitted in a late stage and because of symptoms. Treatment consisted of alkali, fomepizole (71%) and haemodialysis (73%).

Results. The median serum methanol was 25.0 mmol L^{-1} (80 mg dL^{-1}) (range 3.1–147.0 mmol L^{-1}), median pH was 7.20 (6.50–7.50), and median base deficit 22 mmol L^{-1} (range 0–31). The most frequent clinical features reported were visual disturbances (55%), dyspnoea (41%), and gastrointestinal symptoms (43%). Twenty-four per cent were comatose on admission, of whom 67% died. There was a trend towards decreasing pCO_2 with decreasing pH amongst the patients surviving. The opposite trend was demonstrated in the dying; the difference was highly significant by linear regression analyses ($P < 0.001$).

Conclusions. Methanol poisoning still has a high morbidity and mortality, mainly because of late diagnosis and treatment. Respiratory arrest, coma and severe metabolic acidosis (pH < 6.90, base deficit >28 mmol L^{-1}) upon admission were strong predictors of poor outcome. Early admission and ability of respiratory compensation of metabolic acidosis was associated with survival.

Keywords: diagnosis, epidemiology, methanol poisoning, prognosis, symptoms.

Introduction

In spite of improved treatment, morbidity and mortality in methanol poisoning remains high, mainly because of an often difficult, and therefore delayed, diagnosis [1]. Treatment consists of buffer to correct the metabolic acidosis, and antidote to inhibit the metabolism of methanol to its toxic metabolite formic acid. If necessary, haemodialysis is applied to further correct the acidosis, and remove both methanol and formate [2, 3]. In addition, folinic acid may enhance the metabolism of formate [4, 5], but there is no clinical evidence in humans [2].

In the present outbreak, all the liquor probably came from the same origin in southern Europe and contained approximately 20% methanol and 80% ethanol. The liquor was illegally taken into the country and sold in plastic cans of approximately 10 L, and some were later bottled looking much like different kind of original bottles. Price level of commercially available alcohol in Norway seems to

be the main reason for illegal alcohol consumption. This methanol outbreak developed to be a large criminal case with charges of murder to some of the distributors of the liquor.

Methanol poisoning is a classic example of a life-threatening condition where species differences prevent us from getting information from experimental studies [6]. Only certain primates and animals made folate deficient have been used as models [4, 5]. Other species do not develop acidosis or toxicity from methanol exposure. Therefore, most of our knowledge is based on case series studies and only one controlled trial [7]. Because of this, this outbreak is hitherto the largest where both serum-methanol, acid-base-status and in some cases, even serum-formate were measured. This is also the first large-scale outbreak in which fomepizole has been used as an antidote.

We have addressed the general epidemiology, clinical features, treatment and prognostic signs in this methanol outbreak.

Material and methods

Patients and procedures

Fifty-one patients with a median age of 53 years were admitted from September 2002 until December 2004, of whom 33 were admitted in 2002, 13 in 2003 and five in 2004. Nine patients died in hospital (hospital mortality 18%), two of these became organ donors. Five patients were discharged from hospital with sequelae (10%), whereas one died 1 year later from cerebral sequelae. Eight patients who died outside hospital were diagnosed as methanol poisonings on autopsy (Fig. 1). This is probably a minimum figure, as more patients could be expected to die without the diagnosis of methanol poisoning being suspected. As methanol in these cases may be completely metabolized, the only way to diagnosis would be to perform formate analyses. This was performed in the eight patients mentioned above. The time span gave us an opportunity to rapidly establish protocols for diagnosis and treatment of the methanol-poisoned patients.

The patients were retrospectively separated into three groups according to the outcome: group I, the patients who survived without sequelae; group II, the patients who survived with sequelae; group III, the patients who died.

Treatment

Patients were given buffer (bicarbonate or trometamol; Tribonat®, Baxter Deutschland GmbH, Plattling, Germany) aiming at a full correction of acidosis within the first hours. In addition, they were given ethanol (15 patients) or fomepizole (36 patients) as antidotes, and haemodialysis (37 patients). Fomepizole (Fomepizole®, OPi Orphan Pharma International, Paris, France) was given as a bolus dose of 15 mg kg^{-1} i.v. diluted in isotonic saline, and then 10 mg kg^{-1} every 12 h, all doses given over 30 min. From the fifth dose and on, 15 mg kg^{-1} was given in order to compensate for increased metabolism [8]. During dialysis, 10 mg kg^{-1} fomepizole was given every 4 h.

Treatment was given according to the standard protocols, and in accordance with the Helsinki Declaration. Analyses were performed from blood samples already drawn for treatment purposes. If additional blood samples were drawn, permission was obtained from the patients who were awake or from relatives if the patients were unconscious. This procedure was approved by the Regional Ethics Committee.

Laboratory investigations

Methanol in serum was measured by a gas chromatographic method with flame ionization detection and a headspace injector (Fisons GC 8000; Rodano, Italy) (sensitivity 1.3 mmol L^{-1} and day-to-day coefficient of variation 5%). Calibrators and controls were made by dilution of 100% methanol (Merck, Damstadt, Germany). After blood collection, samples were spun and frozen (−20 °C) until analyses.

Statistical analyses

Comparisons between the admission data in the different groups were initially performed by the use of Kruskal–Wallis nonparametric test. The statistically significant parameters were then compared group by group using Mann–Whitney *U*-test. At last, the significant parameters were separated by 25-, 50- and 75-percentiles in order to look for possible threshold values for the different parameters. The correlation between pH and pCO_2 was performed by interaction term using regression analysis.

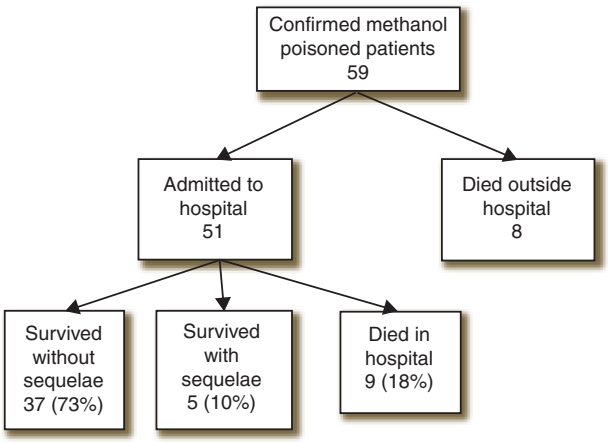

Fig. 1 Methanol accident in Norway 2002–2004.

Results

There were 39 males and 12 females (Fig. 2). Median S-methanol in all the groups on admission was 25.0 mmol L^{-1} (80 mg dL^{-1}) (range 3.1–147.0 mmol L^{-1}) (Table 1). Of those 39 (77%) who were symptomatic upon admission, 28 patients (55%) presented with visual disturbances, 21 (41%) with dyspnoea, 22 (43%) with gastrointestinal (GI) symptoms, 12 patients (24%) were comatose, six (12%) with chest pain and eight (16%) with other symptoms (mainly fatigue). Eight patients (16%) were presented with respiratory arrest (Table 1). Also included are symptoms prior to admission in those cases where information was obtainable from anamnesis.

Seven patients had detectable ethanol before further antidote treatment was given, with a median concentration of 9 mmol L^{-1} (41 mg dL^{-1}) (range 2–48 mmol L^{-1}) (Table 1). In addition, 10 patients were not analysed for S-ethanol before ethanol treatment were given, hence more than seven could possibly have had detectable S-ethanol.

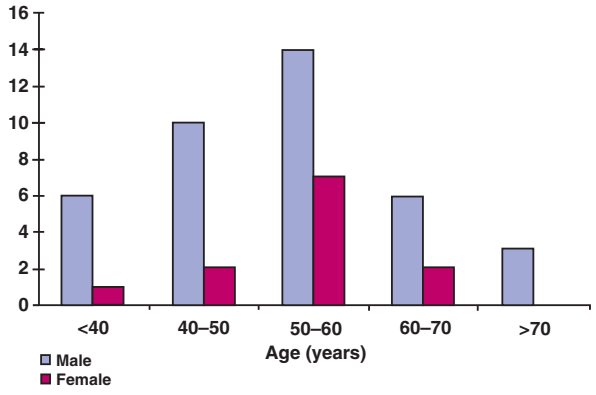

Fig. 2 Age and gender of the methanol-poisoned patients admitted to hospital.

Amongst five patients who were discharged with sequelae, of whom all had visual sequelae, two were comatose on admission, hence their visual status before admission was not known. Therefore, only 3 of 28 (11%) who, with certainty, presented with visual disturbances were discharged with visual sequelae. Sixty per cent of the patients discharged with sequelae had visual disturbances on admission, 40% had GI symptoms, dyspnoea, coma and respiratory arrest (Table 1).

As illustrated in Table 1, respiratory arrest and coma on admission were robust markers of poor outcome: six of eight (75%) patients admitted with respiratory arrest died and eight of 12 (67%) comatose patients died (89% of the patients who died were comatose on admission), two of 12 (17%) were discharged with sequelae, and two of 12 (17%) were discharged without sequelae.

Although the patients with the most severe outcome also had the highest S-methanol (Table 2), the differences between the groups surviving without sequelae, surviving with sequelae, and the patients who died, were not significant ($P = 0.289$, using Kruskal–Wallis nonparametric test) (Fig. 3a). The patients who died were more acidotic [median pH 6.57, median base deficit (BD) 28 mmol L^{-1}] than the patients discharged with sequelae and those discharged without (Table 2). There was a significant difference between these three groups regarding pH ($P < 0.001$) (Fig. 3b), and BD ($P = 0.001$) (Fig. 3c), but not regarding HCO_3^- ($P = 0.207$) (Fig. 3e) using Kruskal–Wallis

Table 1 Laboratory analyses and clinical features on admission in all 51 patients

No	Sex/ age	MetOH (mmol L^{-1})	EtOH (mmol L^{-1})	pH	pCO_2 (kPa)	HCO_3^- (mmol L^{-1})	BD (mmol L^{-1})	AG (mmol L^{-1})	OG[c]	HD (h)	Antidote	Clinical features	Sequelae
1	M/51	3.1	0	7.40	6.0	27	2	ND	ND	0	E	None	None
2	M/67	4.1	0	7.40	5.0	ND	2	ND	6	0	E	None	None
3	F/53	6.3	11[a]	7.21	2.3	5	20	38	29	8	E	VD, GI	None
4	M/34	6.3	0	7.39	4.2	19	5	22	8	0	E	None	None
5	M/38	6.8	0	7.20	1.7	9	24	41	ND	9	F	VD, D, GI	None
6	F/59	8.1	0	7.40	5.1	ND	1	ND	13	0	E	None	None
7	M/35	8.4	9[a]	7.26	2.5	8	17	28	24	0	F	VD, D, CP	VS
8	F/31	8.8	0	6.34	9.5	4	ND	48	49	6	F	VD, D, GI, F, C, RA	Died
9	M/48	9.4	48	7.40	4.8	22	2	24	14	0	E	None	None
10	F/43	9.4	0	7.12	1.7	5	9	28	18	4	F	VD, D, GI	None
11	M/59	9.4	11[a]	7.17	2.0	3	23	32	30	8	E	VD, GI	None
12	M/44	9.4	0	7.29	2.8	10	15	31	9	10	F	None	None
13	M/44	12.5	0	7.22	2.8	6	21	32	20	8	E	VD, D, F	None
14	M/38	12.5	0	7.19	1.3	4	24	35	34	7	F	GI, F	None
15	M/48	12.5	0	7.25	2.3	7	17	30	29	0	F	VD, D, GI	None
16	M/45	12.5	ND	7.25	2.7	12	17	26	23	3 + 10	F	VD, GI, F	None
17	M/40	12.5	4	7.37	5.5	23	1	16	17	0	E	None	None
18	M/72	15.6	0	7.25	2.2	7	20	39	14	3	E	D	None
19	F/69	15.6	0	7.12	1.6	4	25	34	21	4	F	VD, D, GI, F	None
20	F/54	15.6	0	6.92	1.9	3	30	40	16	5	F	VD, D, CP	None
21	F/54	15.6	13[a]	6.51	7.2	4	29	39	51	8	F	VD, C	Died
22	M/52	15.6	7[a]	7.38	2.7	12	11	27	28	0	F	VD	None
23	M/46	18.8	0	7.23	1.9	6	19	39	25	0	F	VD, D, CP, GI	None
24	M/70	21.9	13[a]	7.12	2.4	6	22	30	24	0	F	VD, GI	None
25	M/63	23.4	0	7.13	2.0	5	24	ND	56	3	F	VD, D, GI	Died
26	F/57	25.0	0	6.66	4.3	1	29	50	53	6	F	C, RA	VS, CS
27	M/52	27.0	2	6.50	15.9	10	25	39	53	0	E	VD, GI, C, RA	Died
28	M/55	28.0	0	7.22	1.9	6	21	ND	ND	7	F	D, CP	None
29	F/57	31.2	ND	7.37	4.3	20	1	13	35	0	F	None	None
30	M/49	31.3	0	7.15	1.4	4	25	42	22	6	F	VD, D, PP	None
31	M/41	32.5	0	6.87	2.9	4	29	40	61	8	F	VD, D	VS, CS
32	M/35	33.8	20[a]	7.27	3.6	12	13	25	50	6	F	VD, D, GP	None
33	F/65	34.4	15[a]	6.85	1.9	2	28	50	36	6	F	GI, CP, C, RA	None
34	F/59	46.6	0	6.55	9.3	ND	28	40	87	8	F	C, RA	Died
35	M/75	65.0	0	6.91	2.6	4	30	45	78	6	E	GI, D	None
36	M/57	68.8	7[a]	7.09	1.6	3	25	ND	ND	11	E	VD, GI, D, F	None
37	M/64	68.8	0	7.00	3.0	7	24	30	80	8	F	VD, GI, F	VS, CS
38	M/54	71.9	0	7.12	1.3	3	27	31	84	5	E	VD, GI	None
39	M/51	75.0	ND	6.73	4.8	5	31	37	ND	0	E	VD, D, C, RA	Died
40	F/58	75.0	0	7.06	2.1	4	24	35	82	7	F	VD, D, GI, F	None
41	F/46	76.3	0	6.62	4.3	3	ND	30	94	5	F	VD, C, RA	Died
42	M/62	77.5	0	6.60	6.1	5	28	39	113	8	F	CP, C, RA, PP	VS, CS[b]
43	M/52	84.4	0	6.86	2.1	3	28	33	124	7.5	F	F, C	None
44	F/42	96.9	24[a]	7.40	5.3	23	0	16	134	8	F	VD, GI	None
45	M/69	102.8	0	7.33	3.9	15	9	24	101	8	F	None	None
46	M/63	103.1	0	7.35	2.1	14	11	26	106	9	F	D, GI	None
47	M/36	109.0	4	7.45	5.0	26	ND	22	92	8.5	F	None	None
48	M/59	128.1	11	6.57	7.9	5	28	53	152	7 + 4	F	C, RA	Died
49	M/53	140.6	9	7.50	4.8	28	5	23	138	8	F	None	None
50	M/53	146.9	0	6.90	7.9	5	28	47	159	9	F	VD, D, GI, C	Died
51	M/45	147.0	20	7.42	5.7	27	3	ND	122	10 + 4	F	None	None
Median	53	25.0	0	7.20	2.8	6	22	33	43	6			

MetOH, methanol concentration; EtOH, ethanol concentration; BD, base deficit; AG, anion gap; OG, osmolal gap; HD, haemodialysis; VD, visual disturbances; D, dyspnoea; CP, chest pain; GI, gastrointestinal symptoms; F, fatigue; C, coma; RA, respiratory arrest; PP, pseudo papillitis; VS, visual sequelae; CS, cerebral sequelae.
[a]Treated with ethanol before analysis. [b]Died after 1 year. [c]mOsm/kgH_2O.

nonparametric test. The statistically significant parameters in Fig. 3(b–d) were compared group by group using nonparametric Mann–Whitney *U*-test (see figure text).

In Figure 4(a–c), the three groups in Figure 3 were further separated by the 25-, 50- and 75-percentiles, in order to look for possible threshold values regarding different prognosis. Note that the 25-percentile (pH below 6.90) almost completely separated the dying patients (group III) from those surviving (group I) (Fig. 4a). The one patient (patient 25, Table 1) dying in the 50-percentile group (pH 6.90–7.19), was admitted with the tentative diagnosis of stroke and methanol poisoning was therefore diagnosed late. He is therefore an outlier amongst the dead (pH 7.13, pCO_2 2.0 kPa). This patient also explains one of the two deaths in the 50-percentile of the BD values in Fig. 4b, which without him would distinguish survivors well at a BD <28 mmol L^{-1}.

Amongst the patients surviving, there was a trend towards decreased pCO_2 when pH was decreasing, whilst the trend was opposite amongst the patients dying (Fig. 5), the difference between groups being highly significant ($P < 0.001$). The association between death and having the highest pCO_2 is also reflected in Figure 4c.

In 13 of the dialysed patients, serum methanol levels were obtained before start of, and after termination of, haemodialysis (Fig. 6). During dialysis the mean half-life of the serum methanol concentration was 2.4 h.

Discussion

As is evident from this study, methanol poisoning still has a high mortality in spite of improved treatment [2]. This is mainly because of late hospitalization and diagnosis. Poor outcome is here clearly correlated to the degree of metabolic acidosis, i.e. the amount of formic acid – and later lactic acid (not shown in this study) – produced from methanol metabolism and formate inhibition of mitochondrial respiration respectively [9]. Early diagnosis and subsequent treatment is therefore crucial in epidemics like this. Diagnosis was delayed in some of our patients because physicians was not trained properly in the use of osmolal and anion gaps in the lack of methanol or formate analyses [9]. Only a few centres receiving the present patients were able to perform methanol analyses on a 24-h basis.

Most of the patients were symptomatic upon admission (77%), and amongst these 72% reported visual disturbances, making this the single most frequent clinical feature. The present findings are also confirmed in other studies, reporting visual disturbances in 29–64% of all [7, 10–12]. GI symptoms and signs are also reported frequently in 18–67% [11–13]. Regarding dyspnoea, this symptom is reported with less frequency, 8–25% [11, 13], than amongst the present patients. The reason for the relatively high number in our material, might be because our present definition of dyspnoea, including hyperventilation and 'lack of breath'.

In the present epidemic, our experience with fomepizole was good. The metabolism of methanol was effectively blocked, and compared with our earlier experience with ethanol, fomepizole was easier to administer and there was no need for therapeutic drug monitoring [7, 14]. Fomepizole caused no respiratory depression and many patients could be treated outside the ICU or only needed a brief stay. Fomepizole is expensive [for a 70-kg patient, the average price in Scandinavia is approximately €7800 for a 3-day treatment (six doses)], but the spared ICU costs, sober patients and less need for dialysis [3] may balance these expenses. In the present outbreak, the problems with the costs and shorter shelf-life of fomepizole compared with ethanol were solved by stock-keeping in regional centres. If fomepizole was not available at once, the patients were treated with ethanol until fomepizole was obtained.

Table 2 A median value of serum analyses and number of comatose patients in the different groups

Group	Age (years)	MetOH (mmol L^{-1})	EtOH (mmol L^{-1})	pH	pCO_2 (kPa)	BD (mmol L^{-1})	HD (h)	Coma at admission
Dead	53	46.6	0	6.57	7.9	28	6	8/9 (89%)
Sequelae	57	32.5	0	6.79	3.0	28	8	2/5 (40%)
No sequelae	52	15.6	0	7.25	2.4	18	6	2/37 (5%)

MetOH, methanol concentration; EtOH, ethanol concentration; BD, base deficit; HD, haemodialysis.

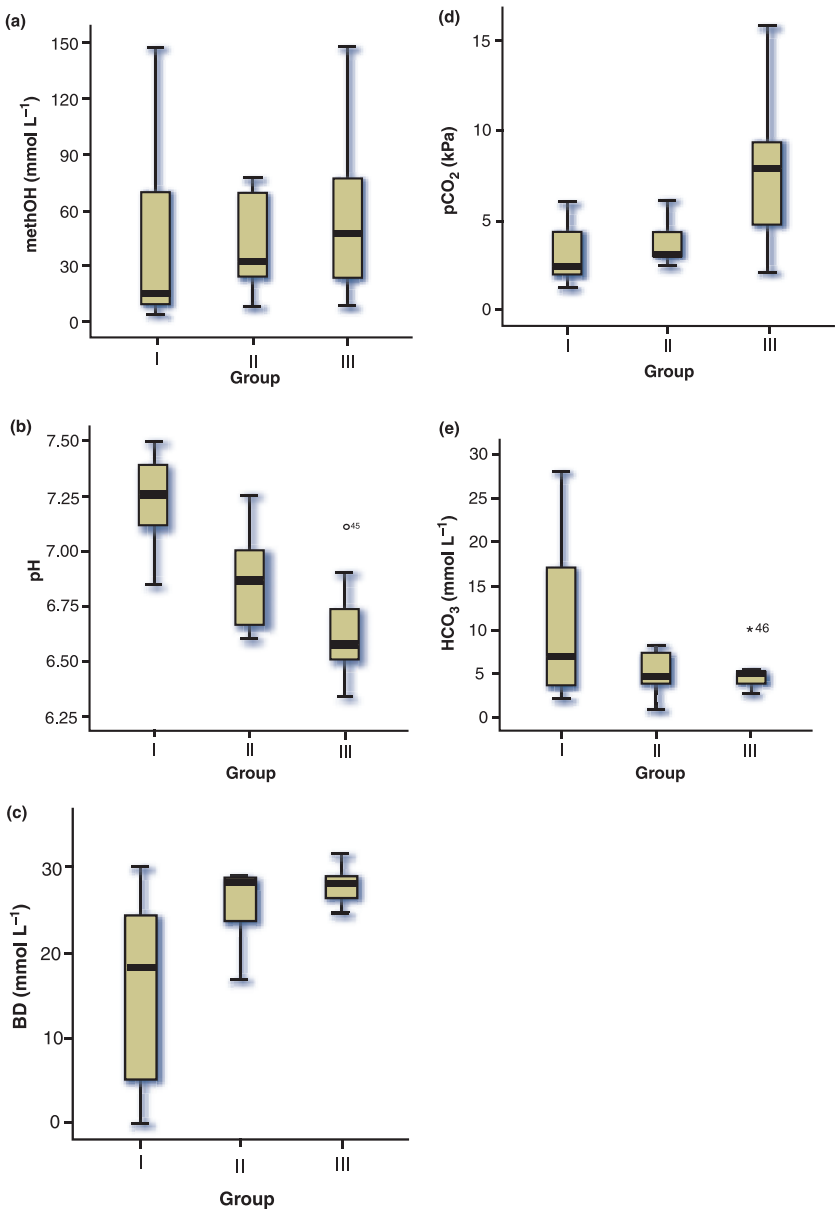

Fig. 3 Box-and-whisker plot of the different groups. The box indicates the 25-, 50- and 75-percentiles, and the points at the ends of the 'whiskers' are the 2.5% and 97.5% values. Group I: survived without sequelae, group II: survived with sequelae, group III: died. Initially, all statistics was calculated by the use of Kruskal–Wallis (KW) nonparametric test. Thereafter, the significant parameters were separated and individual significance was calculated by Mann–Whitney *U*-test (MWU). (a) Methanol concentration in the different groups. No significant difference ($P = 0.289$, KW). (b) pH in the different groups. There were significant difference ($P < 0.001$, KW) between groups I and II ($P = 0.001$) and groups I and III ($P < 0.0005$), but not between groups II and III ($P = 0.096$) (MWU). (c) Base deficit in the different groups. There were significant difference ($P = 0.001$, KW) between groups I and II ($P = 0.038$) and groups I and III ($P = 0.01$), but not between groups II and III ($P = 0.46$) (MWU). (d) pCO_2 in the different groups. There were significant difference ($P = 0.001$, KW) between groups I and III ($P = 0.01$), but not between groups I and II ($P = 0.14$) and groups II and III ($P = 0.053$) (MWU). (e) HCO_3^- in the different groups. No significant difference ($P = 0.207$, KW).

Although our experience with fomepizole was good, ethanol was also an effective antidote. This is illustrated by the delayed onset of symptoms in the present population, and the fact that five of seven patients presented with detectable ethanol levels (patients 9, 17, 47, 49 and 51) were not acidotic despite having two of the highest methanol concentrations (patients 49 and 51). We have no

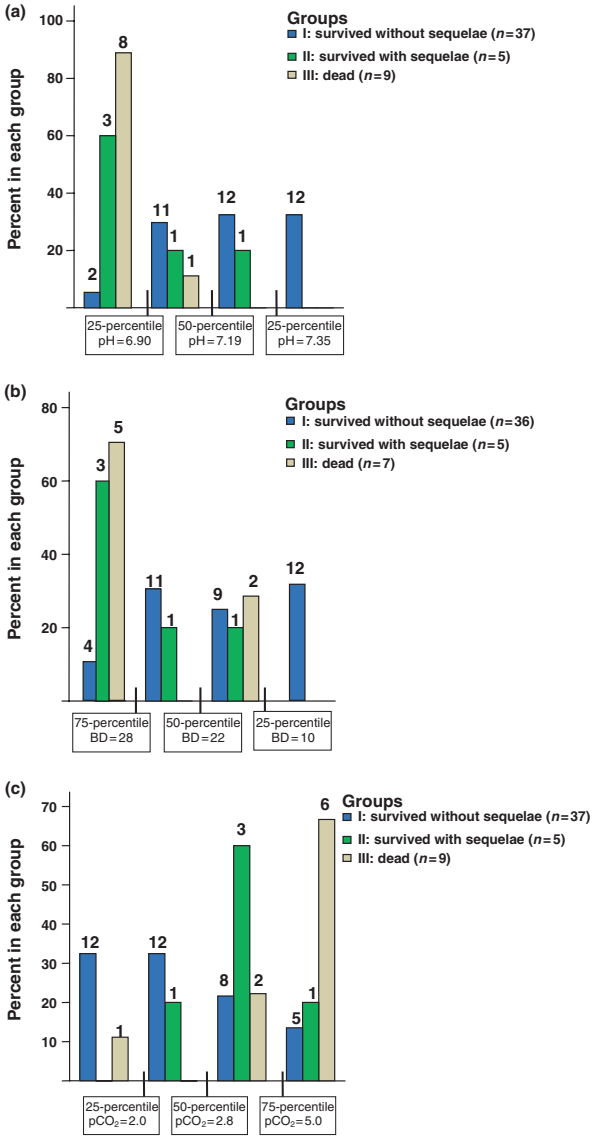

Fig. 4 The three parameters with significant differences from Fig. 3(b–d) categorized by the 25-, 50- and 75-percentiles. Numbers above the columns represent exact number (n) in each group. Confounders are few patients in groups II and III (5 and 9 patients respectively). 25-, 50- and 75-percentiles of the pH (a), BD (b) and pCO_2 (c) in the different groups.

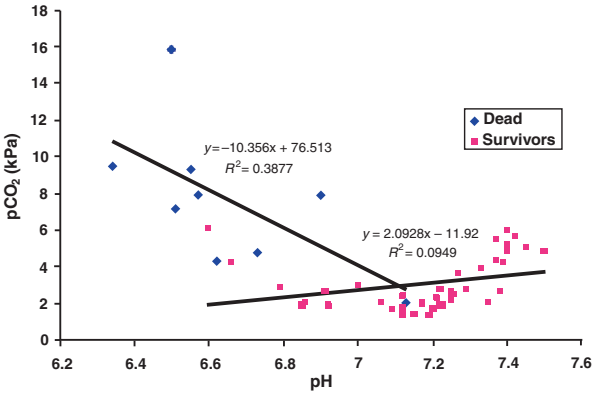

Fig. 5 Ability to ventilate as a prognostic sign. pH versus pCO_2 in the dead versus the survivors. The interaction term was significant ($P < 0.001$) using regression analysis.

explanation why this was not the case in patients 27 and 48 who both presented with severe metabolic acidosis and died. As ethanol was the preferred antidote in case 27, ethanol infusion might have started before sampling, but this is not likely according to the hospital records. In patient 48, the molar concentration of ethanol was much lower than the recommended 25% of the molar concentration of methanol [1]. The ethanol level was therefore theoretically subtherapeutic in this case, however, not in case 49 with a similar molar ratio between serum ethanol and methanol level. This may in part be explained by inter-individual differences, but it is highly unlikely that patient 48 has achieved a pH of 6.57 in the few hours from therapeutic doses of ethanol (32 mmol L^{-1}) until the admission sample was taken (11 mmol L^{-1}). Therefore, the most likely explanation in patients 27 and 48 is intake of additional smuggled spirit or other ethanol just before admission, i.e. after metabolic acidosis had developed.

One could postulate that the present ethanol/methanol mixture would give a better outcome or prognosis, as an antidote was also ingested (e.g. patients 49 and 51). However, this delayed the onset of symptoms and made it difficult to relate these to the intake of the liquor. Many of the patients were alcoholics and interpreted the symptoms of methanol poisoning as alcohol withdrawal. Therefore many drank more ethanol or smuggled spirit and thereby treated themselves. This fact made diagnosing even more difficult, especially if based on a history from the patient.

As mentioned, many of the present patients were alcoholics. This contrasts the former outbreak in this country where many patients were students admitted to hospital mainly because of recommendation through the media, most before symptoms had developed. They were therefore less seriously poisoned as reflected by their less severe metabolic

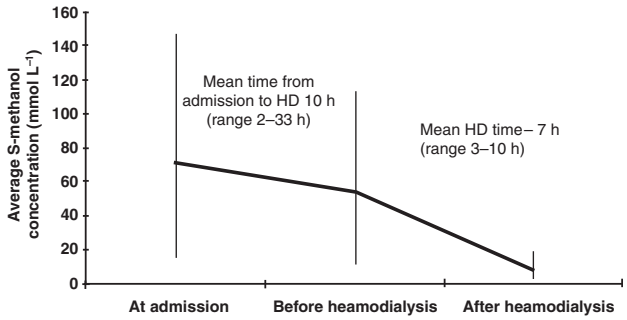

Fig. 6 Mean serum methanol concentration at admission, before haemodialysis (HD) and after HD in 13 patients. The vertical line represents the range of S-methanol measured, the horizontal line represent the mean serum methanol concentration before and during dialysis.

acidosis, and their better outcome with only three deaths (two outside hospital) in 33 patients [2]. This underlines the importance of informing local media and health authorities when dealing with methanol-poisoned patients, especially if the source is unknown or known to be contaminated ethanol.

The mean half-life of serum methanol of 2.4 h during dialysis (Fig. 6) corresponds well with the earlier published material, but comparison is difficult unless proper antidote treatment is given [15]. Before dialysis, there was a varying time before antidote treatment was initiated. No kinetic data could therefore be extracted from this observation period. The reason why some patients waited up to 33 h before dialysis was the effect of fomepizole treatment [3]. In patients with high serum methanol and little or no acidosis (e.g. patients 47 and 51), dialysis was carried out electively without need for triage against other patients needing emergency dialysis.

In methanol poisoning, the prognosis depends on the degree of metabolic acidosis [2, 15], as also illustrated in the present series (Table 2). Although the most severely poisoned patients also had the highest S-methanol in our material, as also seen in one other study [10], the difference was not statistically significant (Fig. 3a). Theoretically, there should be an inverse relationship here: the most severely poisoned patients should have a low methanol level because most of the ingested methanol is metabolized to formic acid [9]. Repeated intake of the present liquor over time could explain high methanol concentrations because ethanol was also ingested preventing methanol metabolism. The repeated periods of methanol metabolism to formic acid (no ethanol present in patients) most probably caused further folate depletion in these patients [1]. This could increase formate accumulation by reduced metabolism and thereby increase formate inhibition of mitochondrial cytochromes, and further increase lactic acid production as demonstrated in some of these patients [9]. Intake of the present alcohol mixture could therefore theoretically explain why the patients with the highest methanol levels also were the most acidotic. Finally, the total amount of methanol ingested will be of importance.

It appears that a pH below 6.90 (the 25-percentile) separates the patients dying (group III), from those surviving without sequelae (group I) (Fig. 4a, the outlier patient 25 is accounted for in results). The only two patients (patients 33 and 43) surviving without sequelae and with a pH < 6.90, had very low pCO_2 (1.9 and 2.1 kPa) indicating excellent ability to compensate their metabolic acidosis by hyperventilation. BD above 28 mmol L^{-1} (75-percentile) also separates between groups I and III (Fig. 4b), but still 30% of the dying patients had a BD between 22 mmol L^{-1} (50-percentile) and 28 mmol L^{-1} (75-percentile). One of these two is the outlier (patient 25), whilst the other patient (patient 27) was not able to hyperventilate, and like the other five dying patients where BD was obtained, he had a significantly elevated pCO_2 (15.9 kPa), i.e. a combined metabolic and respiratory acidosis. Therefore, in our material, lethal outcome seems to be correlated to severe metabolic acidosis with a magnitude of pH < 6.90 and a BD > 28 mmol L^{-1}, and lack of ability of respiratory compensation of severe metabolic acidosis.

None of the patients who died (except patient 25) had a pCO_2 below 2.8 kPa (50-percentile), and the majority (67%) of group II (survivors with sequelae) also seems to have pCO_2 above this (Fig. 4c). Compared with the survivors, the dying patients had a significantly higher pCO_2 at a similar pH. Either the dying patients were not able to hyperventilate in spite of the metabolic acidosis

(Fig. 5), or, this was the actual cause for them to die, i.e. their higher pCO_2 reflected start of central nervous system (CNS) depression of respiration. Confounder here is a more pronounced acidosis amongst the patients dying, and hence the two groups do not overlap completely (Fig. 5).

Another way to look at Fig. 5 is to assume that the combined data from the survivors and the dying patients represent a 'J-curve' where a pH around 6.85–7.10 represents the pH-area where maximum compensatory hyperventilation occurs. At lower pH the condition deteriorates – with further CNS depression – reflected by increasing pCO_2 because of less ability to compensate metabolic acidosis by hyperventilation. The reason for the spread in deaths to the left of this pH-range most probably reflects underlying health/disease of the individual patient – and type of treatment given and how fast it was initiated.

Coma on admission or shortly after has been associated with poor prognosis in methanol poisoning [16]. In total, 12 of 51 (24%) patients were comatose on admission, of whom eight (67%) died. Most other studies reports similar findings. One could expect that age may be an important prognostic factor, but except for the present study, where the patients are older (mean 52 years, range 31–75), other studies had a more comparable age [7, 12]. The study with identical mortality rate amongst the comatose patients as in our series (67%), even had the youngest patients (mean 23 years, range 17–39) [17]. Amongst our dead patients, eight of nine (89%) were comatose on admission. Again the outlier (patient 25) is the exception, as he was the only dying patient conscious on admission. Amongst the survivors without sequelae, only two of 37 (5%) of the patients were comatose on admission.

In our material, the mortality rate amongst the hospitalized patients was 18% (Fig. 1). The mortality rate in other studies shows a more than 10-fold variation, mainly depending on time from intake to admission, concomitant ethanol consumption and hence degree of metabolic acidosis; 14% [17], 17% [13], 36% [18], 3% [11] and 13%, of whom approximately 50% of the latter patients died before admission or within the first 30 min [19]). As illustrated in our series (Fig. 1), and in another [11], those found dead from methanol poisoning outside hospital should also be included to better document the severity of this condition.

Conclusions

During large methanol outbreaks like the present one, information through media plays an important role in warning potentially poisoned patients, and also physicians. Methanol poisoning still has a high mortality, mainly because of delayed admission to hospital and late diagnosis. The use of buffer, antidote and haemodialysis is efficient if initiated early, and methanol poisoning must therefore always be considered in patients presenting with metabolic acidosis of unknown aetiology. Visual disturbances, dyspnoea (including hyperventilation) and GI symptoms were the most frequent clinical features, whilst severe metabolic acidosis ($pH < 6.90$, $BD > 28$ mmol L^{-1}), coma and increased pCO_2 (lack of compensatory hyperventilation) were associated with poor outcome. Most of the patients who presented with symptoms were discharged without sequelae. This is an oft-reported finding seen when proper treatment is initiated in an early symptomatic stage.

Conflict of interest statement

Knut Erik Hovda, Odd Helge Hunderi and Dag Jacobsen have received payment for a lecture on methanol poisoning from Swedish Orphan, the distributor of fomepizole. No conflict of interests from the other authors.

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