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ARTICLE

Methanol mass poisoning in Estonia: Outbreak in 154 patients

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Background. Knowledge of methanol toxicity is based on human data from case series and larger outbreaks. In many of these cases, however, diagnosis was not verified by methanol determinations. We present epidemiological and clinical data from one of the largest methanol outbreaks in which all patients had detectable serum methanol levels. *Methods*. Retrospective case series study of hospital and forensic charts from the five hospitals where patients were treated. *Results*. Of the 147 patients admitted with suspected methanol poisoning, the diagnosis was confirmed in 111, of whom 25 (23 %) died. In addition, 43 patients died outside the hospital, giving a total of 154 patients and a death toll of 68 (44 %). Outcome was related to the degree of metabolic acidosis, serum methanol concentration, coma upon admission, and the patient's ability to hyperventilate. Patients were treated with bicarbonate (85 %), ethanol (87 %), hemodialysis (71 %), and mechanical ventilation (61%) according to clinical features and blood gases, since serum methanol concentrations were analyzed retrospectively. Twenty patients (18 %) survived with permanent sequelae, 18 suffered from impaired vision, and 3 developed permanent brain damage. *Discussion*. Given limited resources, triage and use age of tertiary care centers allowed a small community hospital to treat a high number of methanol-poisoned patients. Critical resources were ventilators and dialyzing machines, whereas stores of antidote (ethanol) and bicarbonate were sufficient. Many patients were mechanically ventilated by hand and treated with bicarbonate and ethanol during transport to tertiary care centers for hemodialysis.

Keywords Methanol poisoning; Epidemiology; Symptoms; Treatment; Prognosis

Introduction

Methanol poisoning is characterized by increasing metabolic acidosis secondary to accumulation of the toxic metabolite formic acid, visual disturbances, and respiratory and cardiovascular failure (1,2). Methanol is metabolized by alcohol dehydrogenase to formaldehyde and further to formic acid, which is primarily responsible for the toxicity in methanol poisoning (3). Metabolism and elimination of formate is folate dependent. Due to a small folate pool in humans (2), formate accumulates. Because of their high folate pool in the liver, only 'nonprimate animals' are able to metabolize formate rapidly. Therefore, only non-human primates represent a good, albeit expensive, animal model (expensive in terms of money and societal influences).

Methanol poisoning is unusual and may occur as mass poisoning or as individual cases spread over time. Mass poisonings typically occur in countries with high taxes on alcohol, where illegal spirits contain methanol as the only alcohol or mixed with ethanol. In other situations, liquor is contaminated with methanol on purpose (4). Suicide attempts with methanol occur (5), but they are rare.

Methanol poisonings are regularly reported as case reports or smaller case series; reports of larger outbreaks are scarce, especially when it comes to the serum methanol (S-methanol) analyses for verification of the diagnosis (6,7). During fall 2001, 190 patients were involved in a methanol outbreak lasting for a few days in the Southwestern part of Estonia, in an area with approximately 92,000 inhabitants. Retrospectively, we traced clinical and laboratory data, and the results are presented here.

Patients and methods

Patients

During September 9–17, 2001, illegal spirits containing 50 to 100% methanol were sold and consumed in the Pärnu region of Estonia. When the methanol was diluted it was mostly with water, but ethanol was used in a few cases (the numbers consuming the latter are not known). Most patients had a history of normal alcohol consumption and some were regular drinkers. A total of 141 patients were admitted to the local hospital in Pärnu and six were admitted to other hospitals. Of these 147, 36 did not have detectable serum methanol on admission, leaving a total of 111 hospitalized patients with verified methanol exposure. Sixty-eight patients died: 25 in

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the hospital and 43 were found dead from methanol poisoning outside the hospital. Thus, a total of 154 patients had a verified methanol poisoning (Fig. 1). Patients were classified into three groups: those who survived with sequelae, those who survived without sequelae, and those who died (Fig. 1). Age and gender of the patients are given in Figure 2. Most of the patients were males (69%), and the age group between 50 and 60 years was most frequently represented (37%).

The treatment of the patients in Pärnu Hospital was complicated by the hospital being small (a total of 135 beds with 5 combined ICU beds), and lacking equipment for hemodialysis. The large number of patients admitted in a short timespan made triage more difficult (Table 1).

Table 1. Number of patients admitted by date

Date	Total number of hospitalized patients	Number of hospitalized patients with verified S-methanol
09.09.2001	17	16
09.10.2001	39	31
09.11.2001	46	36
09.12.2001	18	12
09.13.2001	12	10
09.14.2001	4	2
09.15.2001	3	1
09.16.2001	5	2
09.17.2001	3	1

Treatment

Upon admission, patients were stabilized according to standard procedures. Bicarbonate was given to achieve a full correction of the metabolic acidosis. Nineteen of the 111 patients with confirmed methanol poisoning were not given bicarbonate because of normal blood gas values. The absence of acidosis in these patients was due to additional ethanol consumption confirmed by a positive ethanol serum sample. For therapy, ethanol was mainly given intravenously (10% ethanol diluted in 0.9% NaCl) and sometimes orally, aiming at a therapeutic concentration of 22 mmol/L (100 mg/dL). No therapeutic monitoring of serum methanol was available. Of the 111 patients admitted with positive serum methanol, 80 were transferred to tertiary care centers for consideration for hemodialysis. Ambulances were the main form of transport (four patients were transported by helicopter). Of the transported patients, 19 (24%) were conscious and 61 (76%) were comatose, intubated and, if necessary, sedated. Of those transferred, 76 were dialyzed, in addition to 3 in Pärnu, giving a total of 79 dialyzed patients. Because results of serum methanol analyses were delayed 24–48 hours, the initial treatment (fluid therapy, mechanical ventilation, etc.) was guided mainly by the severity of metabolic acidosis and the clinical features on admission.

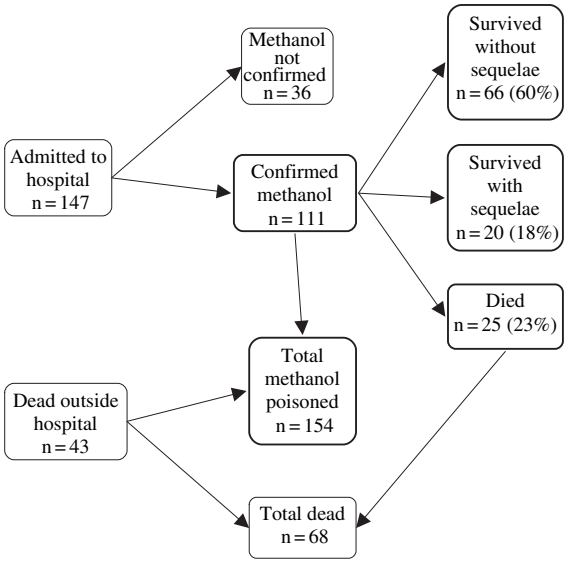

Fig. 1. Algorithm of the patients in the methanol outbreak in Estonia in the fall of 2001.

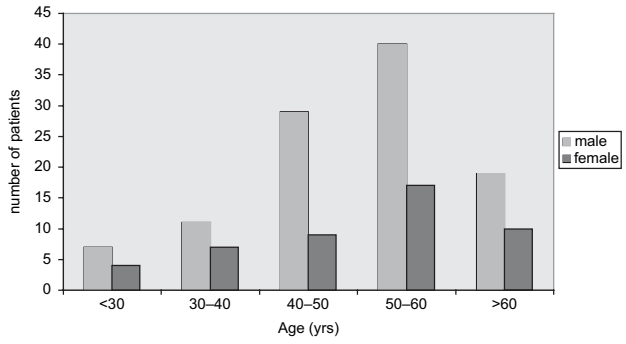

Fig. 2. The age and gender of the 154 methanol poisoned patients.

Methods

Laboratory Investigations

Methanol and ethanol concentration in serum were measured by gas chromatography using a headspace injector (Hewlett Packard chromatograph HP 4890D and Headspace Sampler HP 7694E), and flame ionization detection (GC-FID). Because this chromatograph was replaced by a newer one a few days after the outbreak, exact data on sensitivity and coefficient of variation were not obtained. However, experience from use over years indicated a sensitivity of at least 2 mmol/L for each alcohol (6 mg/dL for methanol and 9 mg/dL for ethanol), and a day-to-day coefficient of variation in the range of 5–10%.

Statistical Analyses

The admission data in the different groups were compared group by group using Mann-Whitney U-test (Table 2).

Table 2. Median S-methanol, S-ethanol, and acid-base status in the verified methanol poisoned subjects

Group	Methanol (mmol/L)	Ethanol (mmol/L)	pH	BD (mmol/L)	pCO_2 (kPa)	HCO_3 (mmol/L)
1	26.6[a] (n = 45, range 1.3–175.0)	2 (n = 14, range 0–91)	7.19[b] (n = 55, range 6.65–7.58)	21[c] (n = 55, range −16–30)	2.6 (n = 54, range 1.2–5.7)	6[d] (n = 50, range 3–41)
2	71.4[a] (n = 8, range 50.3–154.7)	10 (n = 4, range 0–27)	7.14[b] (n = 14, range 6.75–7.53)	22[c] (n = 14, range −2–29)	2.4 (n = 14, range 1.2–4.8)	6[d] (n = 14, range 2–26)
3	110.0[a] (n = 13, range 28.4–194.7)	0 (n = 5, range 0–22)	6.78[b] (n = 18, range 6.64–7.29)	29[c] (n = 18, range 18–30)	3.1 (n = 17, range 1.3–5.5)	4[d] (n = 15, range 2–11)

Blood samples were drawn upon admission. Group 1 represents the patients who survived without sequelae, group 2 the patients who survived with sequelae, and group 3 represents the patients who died. BD = base deficit. Treatment was already initiated before admission to hospital in 46 patients, whereas 14 received prehospital intubations and 32 patients were already given bicarbonate and/or ethanol; all patients are included in this table.
[a]Significant difference between groups 1 and 2 ($p = 0.003$) and groups 1 and 3 ($p < 0.001$), but not between groups 2 and 3.
[b]Significant difference between groups 1 and 3 ($p < 0.001$) and groups 2 and 3 ($p = 0.004$), but not between groups 1 and 2.
[c]Significant difference between groups 1 and 3 ($p < 0.001$) and groups 2 and 3 ($p = 0.005$), but not between groups 1 and 2.
[d]Significant difference between groups 1 and 3 ($p = 0.003$), but not between groups 1 and groups 2 and 3.

Pearson's Chi-square test was used to compare the patients who survived and those who died regarding additional intake of ethanol (Table 3). The correlation between pH and pCO_2 was performed by interaction term using regression analysis (Fig. 3).

Ethics

All the present results are based on blood samples drawn for diagnosis and treatment – no samples were drawn for research purpose only. All patients or relatives gave their informed consent for this procedure, which was accepted by the local ethics committee.

Results

Table 1 presents admitted patients day-by-day and shows number of admitted patients who had positive methanol level in the admission blood sample. Table 2 presents arterial blood gas analyses and serum methanol concentrations on admission in the three groups. Both serum methanol concentrations and the degree of metabolic acidosis increase with the severity of poisoning. Table 4 lists the clinical features reported upon admission in 95 (86 %) of the patients where this was systematically recorded. The most common symptoms and signs on admission were gastrointestinal symptoms (49%), visual disturbances (37%), and dyspnea (20%). Dyspnea was the only clinical feature more commonly seen in the dying group than in the other groups. The overall mortality was 44% when those dying outside hospital were included (Fig. 1). The main cause of death was multi-organ failure, and autopsies revealed cerebral edema and cerebral hemorrhages as the most common findings.

Table 5 presents the treatment given in all patients. Of the 72 patients who were conscious on admission and given ethanol, 29 (40%) developed coma associated with the bolus infusion of ethanol. Two of these also developed respiratory arrest and needed rapid intubation and mechanical ventilation.

Of the 71 patients given conventional hemodialysis (Fig. 4), 12 died. Eleven patients were dialyzed more than once because metabolic acidosis redeveloped. Eight of 79 patients (10%) received continuous venovenous hemodiafiltration (CVVHD), of whom three died.

Table 3. Outcome in the different groups related to their intake of additional ethanol

Group	Type of sequelae	Ethanol consumption in addition	Not drinking ethanol or unknown	Total
1	–	24/30 (80%)*	42/81 (52%)*	66/111 (60%)
2	Total	4/30 (13%)*	16/81 (20%)*	20/111 (18%)
	Visual	4	14	18
	Brain		3	3
	ARF		4	4
	Hepatitis		2	2
3	–	2/30 (7%)*	23/81 (28%)*	25/111 (23%)
Total	–	30 (27%)*	81 (73%)*	–

Group 1: Survived without sequelae; group 2: survived with sequelae, group 3: died.
ARF = Acute renal failure.
*Significant difference between ethanol and no ethanol in the different groups ($p = 0.018$, Pearson Chi-square).

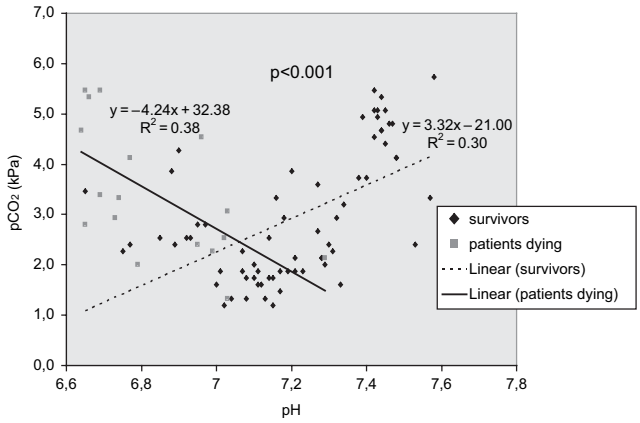

Fig. 3. Arterial pH versus pCO_2 in 93 of the methanol-poisoned patients where parallel measurements were taken on admission. Patients who were intubated before administration are excluded here. The interaction term was significant ($p < 0.001$) using regression analysis.

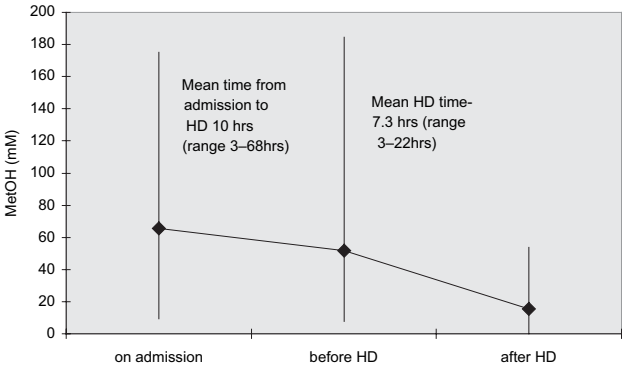

Fig. 4. Median serum methanol concentration on admission, before and after hemodialysis (HD). The vertical lines represent the range of S-methanol measured.

Table 4. Clinical features in the various groups upon admission to the hospital

	Group 1	Group 2	Group 3
GI-symptoms	31/66 (47%)	11/20 (55%)	12/25 (48%)
Visual disturbances	23/66 (35%)	9/20 (45%)	9/25 (36%)
Dyspnoea	13/66 (20%)	2/20 (10%)	7/25 (28%)
Other clinical features	22/66 (33%)	9/20 (45%)	8/25 (32%)
Unknown	1/66 (1.5 %)	2/20 (10%)	4/25 (16%)
None	15/66 (23%)	1/20 (5%)	–

Table 5. Treatment given to the methanol-poisoned patients

	Number of patients
$NaHCO_3$	94 (85%)
Ethanol	96 (87%)
Dialysis	79 (71%)
Mechanical ventilation	68 (61%)
No treatment/ observation only	14 (13%)

$NaHCO_3$ given: Mean 525 mmoles (range 100–1500 mmoles).
Ethanol given: Mean 201g (range 42–500g).

Table 3 presents the outcome and the type of sequelae in the survivors. There were significantly less sequelae and deaths among the 30 patients known to have been drinking ethanol in addition to methanol compared to the other 81 patients ($p = 0.018$, using Pearson's Chi-square).

Figure 4 shows changes in median methanol serum concentrations during hemodialysis. There is an increased elimination during dialysis compared to the time before dialysis. It was not possible to calculate the half-life of serum methanol because there were too few data points in each patient.

Figure 3 shows the correlation between arterial pH and pCO_2 in the patients who died and the patients who survived. There was a trend towards decreased pCO_2 when pH was decreasing among the patients surviving, while the trend was opposite among the patients dying. The interaction term was significant ($p < 0.001$) using regression analysis.

Discussion

As seen from Table 2, mortality increases with increasing degree of metabolic acidosis. This correlation has been reported by other authors (1,8,9). The considerable overlap between the groups was most probably related to the retrospective collection of data and the fact that no monitoring of ethanol therapy was available. The latter probably best explained why one patient died with an admission arterial pH of 7.29, although significant co-morbidity was also present. In the present outbreak, increasing serum methanol concentrations were associated with increasing severity (Table 2). This finding has been described by others (9,10), while some authors find no such correlation (11,12,13). There might be several reasons for this variation in findings, but in the present outbreak the best explanation would be that the most severely poisoned patients may have been drinking the largest amounts of methanol. Although both sexes and all adult ages were represented, the typical overrepresentation of drinking middle-aged males (5) was demonstrated in this outbreak (Fig. 2).

Gastrointestinal features were the most frequently reported complaint upon admission (49%) (Table 4). This is in accordance with an outbreak involving 323 methanol poisoned subjects (6) in which the authors reported nausea and vomiting in 52% and upper abdominal pain in 67%. Others report gastrointestinal symptoms in 67% (9), 41% (4), and 18% (14) of patients. Visual disturbance is another common finding

(1), and this was reported in 37% of patients in the present study (Table 4). Other authors report visual disturbances in 50% (9), 64% (12), 29% (5), 33% (14), and 55% (4) of the patients. The third most common symptom was dyspnea (20%), which is comparable to other studies (8% (15), 15% (14), and in 25% of the acidotic patients (6)); the exception is the last outbreak in Norway, where as many as 41% had dyspnea (4). The permanent sequelae seen in 20 (18%) subjects are also in accordance with other studies (9,10). The acute renal failure was most likely due to hypotension and the hepatitis to alcoholism.

The new antidote fomepizole has proven safe and efficient (12,16,17), and is the first choice as an antidote in many countries. Because fomepizole was not yet a registered product in Estonia, ethanol was the antidote of choice in this outbreak (Table 5). Ethanol is widely available and inexpensive but its disadvantages (18) were clearly demonstrated in the present outbreak. The lack of S-ethanol monitoring might explain why some patients were still acidotic when dialysis was discontinued. Because ethanol is also removed by dialysis, adequate ethanol dosing during this procedure was almost impossible without serum ethanol monitoring (1,2). Since most patients became drunk after the start of ethanol treatment, and because staff resources were limited, patient handling became difficult. In addition, the CNS depressant effect of ethanol was associated with development of coma and worsening of an already marginal respiration (18).

Eight hours of hemodialysis is often recommended if methanol analyses are unavailable (3). The mean length of conventional hemodialysis in the present study was somewhat shorter (6.3 hours, range 3 to 20 hours), mainly because of the high number of patients and limited dialyzing capacity. Both the development of coma and the need for subsequent endotracheal intubation in two patients were temporally related to the start of ethanol administration. Once intubated, however, there were no reports of further complications during transport related to the treatment with 10% ethanol or bicarbonate.

The superiority of conventional hemodialysis over CVVHD (mean duration 15.8 hours, range 13 to 22 hours) regarding removal of methanol has been demonstrated (19). CVVHD was used in this outbreak mainly because of limited access to conventional hemodialysis, but also because some patients were cardiovascularly unstable and might not have tolerated hemodialysis. The limited dialysis capacity also explains why patients had to wait up to 68 hrs before this procedure could be initiated (Fig. 3). Thirty-two patients were not dialyzed because they died very soon after admission because CT scans revealed intra-cerebral bleeding, or because the patients were too ill for dialysis. Not everyone in the latter group could be offered CVVHD because the availability of this advanced treatment also became limited.

Some of the patients had a higher serum methanol concentration after dialysis than generally recommended for terminating this procedure (median S-methanol after hemodialysis: 16 mmol/L (50 mg/dL) (range 0 to 54 mmol/L (0 to 172 mg/dL)) (3,1). Some of these patients were still acidotic at the end of hemodialysis, probably because of a lack of serum ethanol monitoring (median pH 7.40, range 7.11 to 7.55).

Severe metabolic acidosis and coma are related to poor prognosis, while the ability to hyperventilate has been suggested to be a predictor for better outcome (4). The latter finding is supported by the present study, where there was a significant difference in ability to hyperventilate between the patients who survived and the ones who died. The first group had a decreased pCO_2 when pH decreased (i.e., ability to hyperventilate), while the opposite trend was evident in the dying patients (Fig. 3). Whether the dying patients were unable to hyperventilate in spite of the metabolic acidosis or whether their higher pCO_2 reflected the start of CNS depression of respiration is unknown. This interesting observation is probably not related to the ethanol-induced CNS depression because this trend was also seen when the antidote fomepizole was used (4).

Conclusion

The present article describes a large methanol outbreak with many critically ill patients in need of ventilators and dialyzing machines in addition to treatment with alkali and antidote. The use of ethanol instead of fomepizole as an antidote may not have influenced outcome, as many patients with respiratory depression survived on mechanical ventilation by hand or ventilators. Compared to similar patients treated with fomepizole, however, the morbidity was higher and there was more of a need for intensive care resources. This may be especially important in larger outbreaks where such resources are limited.

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Conflict of Interest Statement

Knut Erik Hovda and Dag Jacobsen have received payment for a lecture on methanol poisoning from Swedish Orphan, the distributor of fomepizole in Scandinavia. There are no conflict of interests from the other authors.

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