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Epidemic Acute Methanol Intoxication as a Result of Illicit Alcohol Ingestion

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ABSTRACT

Background: Methanol poisoning, whether sporadic or mass poisoning, is an acute medical emergency. It can lead to considerable morbidity as well as mortality.
Objectives: We retrospectively evaluated 30 cases of methanol intoxication admitted to the nephrology unit of our hospital.
Materials and Methods: We collected demographic data, clinical findings, and laboratory parameters after the study protocol was approved by the local human ethics committee.
Results: Headache, dizziness, nausea, vomiting and visual disturbances were the most common complaints. Twenty-eight patients had high anion-gap metabolic acidosis. Five patients, without toxic optic neuropathy and serious metabolic acidosis, were treated with ethanol and bicarbonate infusions, and improved without requiring hemodialysis (HD). Twenty-five patients, who were admitted with visual disturbances or complete blindness or serious metabolic acidosis, were treated by HD; 7 of these patients (23.3%) died. All of them had blurred vision, were unconscious at presentation, and presented with metabolic acidosis with high anionic gap. No significant differences ($P > 0.05$) were found between patients with and without toxic optic neuropathy, in terms of biochemical parameters and blood gases. The 5 patients with toxic optic neuropathy were treated with oral methylprednisolone and HD. Two patients had complete remission, 2 others improved with total blindness, and 1 died.
Conclusions: We found that unconsciousness and metabolic acidosis in cases of methanol intoxication were associated with an increased risk of mortality. Medical treatment and if necessary, HD, must be started as soon as possible, especially in the presence of mental state changes, visual disturbances, metabolic acidosis and a history of methanol ingestion.

Implication for health policy/practice/research/medical education:
In cases of methanol intoxications, HD should be started immediately if history of methanol ingestion, unconsciousness, and metabolic acidosis are present.

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1. Background

Methanol is a toxic alcohol that may be ingested accidentally or consumed as an ethanol substitute (1). Methanol poisoning, whether sporadic or mass poisoning, is an acute medical emergency. It can lead to considerable morbidity as well as mortality. The serum level of methanol does not correlate with toxicity. Prognosis is correlated with the degree of metabolic acidosis (2, 3).

Exact rates of morbidity and mortality from intoxication are not available. Central nervous system depression, ocular symptoms, and gastrointestinal complaints are commonly reported initial symptoms of methanol poisoning. Lethal doses are thought to range from 30–240 mL; the minimum lethal dose is believed to be 100 mL (1 g/kg) (4-6).

Specific therapeutic measures include correction of

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metabolic acidosis with sodium bicarbonate, administration of enteral or parenteral ethanol to competitively inhibit metabolic breakdown of methanol to formic acid and hemodialysis (HD) to remove the toxic alcohol and its toxic metabolites (7, 8).

2. Objectives

Epidemics of methanol poisoning can be seen as a result of ingestion of illicit alcohol. This study describes our clinical experience in the management of patients with acute methanol intoxication, emphasizing that early identification and prompt management is of prime importance.

3. Materials and Methods

As a result of consumption of illegal alcohol, an epidemic of acute methanol poisoning occured in Istanbul in March 2005. A total of 44 men drank methyl alcohol. Fourteen of these patients was admitted to nearby peripheral hospitals, 30 patients were directed to the Sisli Etfal Hospital, Istanbul. Detailed history was obtained from all of the patients except the two who were unconscious. All of the patients were examined by physicians with experience in internal medicine, ophthalmology and neurology. The initial diagnosis was made based on a clinical history of evidence of intake of alcohols and presence of metabolic acidosis with elevation of the anion gap. Medical records of all hospitalized patients were reviewed retrospectively.

A sample of blood was taken for hemogram analysis, and for determining levels of serum urea, creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), amylase, along with pre- and post-dialysis blood gases and serum electrolyte levels; calcium (Ca), phosphate (P), sodium (Na) , potassium (K) and chlorine were also measured. Unfortunately, serum methanol levels could not be measured in any of the patients, for technical reasons. The anion gap was calculated using the standard formula (Na + K) - (Cl + HCo_3).

Hemodialysis was performed in patients who complained of blurred vision or blindness, and/or had severe metabolic acidosis (pH < 7.20). For HD, a dual lumen femoral catheter, a high-efficiency dialyser made of 1.6 m2 polysulfone membrane, a blood flow of 250–300 mL/min, and a bicarbonate-based dialysate delivery system was used. The dialysate flow rate was kept at 500 mL/min and no net ultrafiltration was obtained. The dialysate contained the following solute concentrations at final dilution; sodium (Na) 138 mmol/L, potassium (K) 3.0 mmol/L, calcium (Ca) 1.25 mmol/L, magnesium (Mg) 0.5 mmol/L, chlorine (9) 110 mmol/L. Hemodialysis was continued until metabolic acidosis was corrected.

To correct metabolic acidosis, all patients were initially infused with 100–300 mL of sodium bicarbonate and 1000 mL of isotonic saline. Oral ethyl alcohol (20%) was used to inhibit alcohol dehydrogenase in patients with methanol poisoning. Oral folic acid was administered to accelerate formate metabolism and serum Na, K, Ca and P were replaced, if necessary. Fomepizole and intravenous (IV) ethanol were not available. For this reason, they could not be used to treat the patients.

Statistical analyses of data was perfromed using the SPSS 11.0 software. All data are expressed as mean and standard deviation. The comparisons were performed using two tests, the unpaired Student's t test for parametric data analysis, and the Mann-Whitney test or Wilcoxon test for nonparametric analysis. A *P* value of <0.05 was considered significant.

4. Results

Thirty patients were admitted to the hospital due to methanol intoxication. All of them were male and the mean age was 41.4 ± 8.5 years. The quantity of the illicit drink consumed was known in all cases, except in the two who were unconscious. It ranged from 200–500 mL. The proportion of methanol to ethanol in the drink was not known. The mean admission time of patients was 31 ± 16 hours (range 8–72 hours). The main complaints at admission were vertigo, dizziness, nausea, vomiting, and visual disturbances. Two patients were unconscious and required mechanical ventilation, and 3 patients had dilated pupils at admission. Toxic optic neuropathy was found in 5 patients on opthalmological examination. The cranial computed tomography (CT) images of the 2 unconscious patients were normal *(Table 1)*.

Twenty-eight patients (mean age, 41.9 ± 8.6 years) had high anion-gap metabolic acidosis, (mean pH, base excess [BE], HCo_3, and anion gap levels were 7.11 ± 0.19, -19.56 ± 7.64, 8.59 ± 3.52, and 28.7 ± 2.4 mmol/L, respectively). Four patients had high levels of ALT and AST (mean ALT, 99.66 U/L; AST, 65.6 U/L; normal range: ALT, 5–34 U/L, AST, 0–55 U/L). Two patients had high levels of amylase (505–624 U/L; normal range, 5–125 U/L) and also high creatinine levels (1.7–2.2 mg/dL; normal range: 0–1.5 mg/dL).

Hemodialysis was used to treat 25 patients (mean age was 41.1 ± 8 years, and mean pH, BE, HCo_3, and anion gap

Table 1. Results of Biochemical Analysis and Blood Gas Parameters

	All Patients (n = 30)
Age, y	41.4 ± 8.49
Admission time, h	31.17 ± 16.36
Urea, mg/dL	27.63 ± 11.20
Creatinine, mg/dL	1.17 ± 0.25
pH	7.13 ± 0.20
Base deficit, mmol/L	-18.34 ± 8.74
Bicarbonate level, mmol/L	9.36 ± 4.66
PCo_2	27.68 ± 13.72
ALT [a], U/L	30.20 ± 9.57
AST [a], U/L	30.47 ± 18.79
Amylase, U/L	68.20 ± 37.99
HD [a] duration, h	9.09 ± 4.32

[a] Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HD, hemodialysis

levels were 7.10 ± 0.20, -19.42 ± 8.41, 8.46 ± 3.79, 33.5 ± 3.2 mmol/L, respectively) with complaints of blurred vision or blindness, and/or severe metabolic acidosis (pH < 7.20). For technical reasons, serum methanol levels could not be determined, and blood gas results were followed instead. Hemodialysis was continued until correction of metabolic acidosis. Correction of metabolic acidosis by HD was achieved as early as 4 hours and occured at 28 hours at the latest (mean, 11.09 hours). Recurent metabolic acidosis was developed in 3 patients after correction of metabolic acidosis by HD. Single HD scans of 7-8 hours duration was performed in 2 of these patients and 16 hours of HD was performed in the other one. Fomepizole is not available in Turkey, and therefore could not be used in the treatment of our patients *(Table 2)*. Hemodialysis was not performed in the 5 patients (mean age, 42.6 ± 11.5 years; mean pH, BE, HCo_3, and anion gap levels, 7.29 ± 0.09, - 12.96 ± 9.24 mmol/L, 13.82 ± 6.47, 23.8 ± 2.6 mmol/L, respectively) without severe metabolic acidosis (pH > 7.20) and toxic optic neuropathy. Oral ethyl alcohol and bicarbonate infusion was performed in these patients. All patients were discharged from the hospital in healthy condition *(Table 2)*.

On detailed ophtalmological examination, 25 patients had changes of varying severity. The changes noted were dilated pupils with or without sluggish reaction to light, hyperemia of the discs, retinal congestion and oedema, blurring of the disc margins, and later on, optic atrophy and varying degrees of loss of vision. Five patients had toxic optic neuropathy. There was no correlation between the ocular changes and the degree of acidosis ($P > 0.05$)*(Table 3)*. Patients with toxic optic neuropathy were treated by methylprednisolone (1 mg/kg) and HD. One of them died. Two of them had complete remission and two patients survived, with total blindness (6.6%).

Seven (23.3%) of the 30 patients with methanol intoxication died. All of them had blurred vision, were unconscious at presentation, and had metabolic acidosis with high anionic gap *(Table 1)*. Among these patients, statistically significant differences ($P = 0.00$) were found in pH, HCo_3 and BE levels, but not in other parameters (admission time, urea, creatinine, ALT, AST, amylase, HD duration) ($P > 0.05$). There was no correlation between hospital

Table 2. Parameters and Laboratory Results of Patients Who Received/Did not Receive HD

	HD [a](+) (n = 25)	HD (n = 5)	*P*
Age, y	41.2 ± 8	41.6 ± 11.6	NS [a]
Admission time, h	29.72 ± 15.29	38.40 ± 21.46	NS
Urea, mg/dL	28.92 ± 11.64	21.20 ± 5.89	0.049
Creatinine, mg/dL	1.20 ± 0.25	1.04 ± 0.08	0,025
pH	7.10 ± 0.20	7.29 ± 0.1	0,005
Base deficit, mmol/L	-19.42 ± 8.41	-12.96 ± 9.24	0,000
Bicarbonate level, mmol/L	8.46 ± 3.79	13.82 ± 6.47	0,032
PCo_2	27.68 ± 13.72	24.26 ± 9.37	NS
ALT [a], U/L	30.12 ± 7.87	31.91 ± 11.51	NS
AST [a], U/L	32.67 ± 17.09	33.80 ± 21.67	NS
Amylase, U/L	67.26 ± 39.23	58.86 ± 36.22	NS

[a] Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HD, hemodialysis; NS, not significant

Table 3. Parameters and Laboratory Results of Patients Who Received Treatment With HD

	Survived (n = 18)	Died (n = 7)	*P*
Age, y	41.04 ± 8.53	42.57 ± 8.94	NS [a]
Admission time, h	32.65 ± 16.72	26.29 ± 15.25	NS
Urea, mg/dL	27.96 ± 12.21	26.57 ±7.63	NS
Creatinine, mg/dL	1.10 ± 0.10	1.42 ±0.41	NS
pH	7.21 ± 0.30	6.86 ± 0.30	0.000
Base deficit, mmol/L	-15.03 ± 6.81	-29.20 ± 4.44	0.000
Bicarbonate level, mmol/L	10.19 ± 4.95	6.61 ± 1.94	0.046
PCo_2	24.26 ± 9.37	38.94 ± 19.88	NS
ALT [a], U/L	30.52 ± 10.41	29.14 ± 6.61	NS
AST [a], U/L	32.80 ± 20.67	22.71 ± 7.06	NS
Amylase, U/L	58.86 ± 37.28	90 ±36.16	NS
HD [a] duration, h	12.03 ± 2.64	10.82 ± 6.58	NS

[a] Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HD, hemodialysis; NS, not significant

Table 4. Results of Biochemical Analysis and Blood Gas Parameters of Patients Who Died

	1	2	3	4	5	6	7
Age, y	41	55	36	45	53	31	37
Admission time, h	16	18	48	24	48	12	18
Methanol level, mg	2	2	0	0	0	366	20
pH	7.11	6.90	6.80	6.87	6.80	6.90	6.65
Base deficit, mmol/L	-23.60	-33.80	-28.3	-23.3	-29.4	-33.9	-32.1
Bicarbonate level, mmol/L	7.10	5.80	5.6	10.2	4	6.1	7.5
Anion gap, mmol/L	36	28	45	28	42	33	45
PCo_2	12.2	25.2	22.2	54.4	45	44	69
Urea, mg/dL	31	25	26	28	23	14	39
Creatinine, mg/dL	1.4	1.7	1.2	1.3	1	1.1	2.22
Amylase, U/L	56	128	46	86	62	56	61
ALT [a], U/L	33	39	32	25	29	28	18
AST [a], U/L	16	38	23	21	21	20	20

[a] Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase

Table 5. Laboratory Results of Patients With or Without Optic Neuropathy

	Optic Neuropathy (+) (n = 5)	Optic Neuropathy (-) (n = 25)	
Admission time, h	28 ± 11.57	31.80 ± 17.28	NS [a]
Urea, mg/dL	30.8 ± 7.69	27.00 ± 11.80	NS
Creatinine, mg/dL	1.24 ± 0.27	1.16 ± 0.25	NS
pH	7.09 ± 0.27	7.14 ± 0.19	NS
Base deficit, mmol/L	-17.78 ± 11.96	-18.45 ± 8.27	NS
Bicarbonate level, mmol/L	8.06 ± 4.04	9.62 ± 4.81	NS
Anion gap, mmol/L	32.3 ± 5.2	29.6 ± 3.8	NS
PCo_2	27.42 ± 11.13	27.74 ± 14.38	NS
ALT [a], U/L	31.2 ± 6.01	30 ± 10.22	NS
AST [a], U/L	27.8 ± 7.56	31 ± 20.38	NS
Amylase, U/L	62.65 ± 35.23	61.56 ± 33.57	NS

[a] Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; NS, not significant

arrival time and the total duration of HD ($P > 0.05$). Methanol levels in blood samples taken during autopsy ranged from 0–336 mg/dL *(Table 4, 5)*. Differences in levels of methanol in blood taken during the autopsy may be due to the HD and late autopsy. The remaining 21 (70%) patients were discharged from the hospital after correction of metabolic acidosis as well as serum creatinine and amylase levels, and satisfactory liver function test results.

5. Discussion

We found that unconsciousness and metabolic acidosis in cases of methanol intoxication were associated with an increased risk of mortality. The toxicity of methanol is clearly correlated with the degree of metabolic acidosis, which is manifested by a low serum bicarbonate level. Formate is assumed to be the toxic agent. In the first step of its degradation, methanol is transformed to formaldehyde via the enzyme alcohol dehydrogenase (ADH). This reaction is slower than the transformation of formaldehyde to formic acid, which may explain the reason for the latency of symptoms between ingestion and effect. It is the formic acid that causes the profound metabolic acidosis that is typical of methanol poisining (10).

Metabolic toxicity becomes apparent followed by a latent period of 12–24 hours (range, 1–72 hours). The symptoms of methanol poisoning are non-specific, except for the visual disturbances. The latent period may be longer if ethyl alcohol is a co-ingestant, or shorter if the amount of methanol is large. In cases of methanol ingestion, a lack of symptoms early on does not mean that the patient has not ingested a toxic amount of methanol (11).

The diagnosis is sometimes elusive and requires clinical investigation. Dependence on serum methanol analysis in methanol poisoning may delay diagnosis and treatment (6, 7). Arterial pH, serum bicarbonate levels, and osmolal and anion gaps can be used as surrogate indicators of the severity of methanol poisoning. These data allow for indirect estimation of methanol poisoning when direct

estimation is not available (12-14). In our patients, the diagnosis depended on an obvious epidemiological context and on the finding of metabolic acidosis with an elevated anion gap.

The eye damage caused by methanol has been well described. The ocular changes correlate with the degree of metabolic acidosis. Visual changes with methanol poisoning are due to microtubule and mitochondrial destruction in the retrolaminar optic nerve (12).

Patients may initially present with blurred vision, with progression to scotomata and scintillations. The frank blindness that develops subsequently can respond to immediate therapy. Even with prompt treatment, however, complete loss of vision is a common sequela. Early visual disturbances are the classic findings that are associated with methanol intoxication and include decreased or blurred vision. Patients may complain of a 'snowstorm' in front of the eyes or photophobia. The pupils may be fixed and dilated in the funduscopic examination, revealing retinal edema with hyperemia of the optic disc. In severe cases, there may be papilledema and engorged retinal vessels (15-17). On detailed examination of the eyes in our patients, as many as 25 patients were found to have optical changes of varying severity *(Table 3)*. Patients with toxic optic neuropathy were treated by methylprednisolone (1 mg/kg) and HD. One of them died, 2 had complete remission, and 2 patients survived, with total blindness.

Central nervous system symptoms are common and include headache, dizziness, feelings of weakness, and malaise (18). Larger amounts of methanol ingestion can result in seizures, stupor, and coma. Bilateral necrosis of the putamen is the most well-known sequela of methanol intoxication that can be identified on CT and magnetic resonance (MR) imaging. These characteristic changes can be seen if the patient survives for longer than 24 hours. Discrete regions of necrosis have also been described in the white matter of patients surviving longer than several days (19, 20).

Two of our patients were unconscious during the physical examination. The initial cranial CT scans of these 2 patients were normal. A second CT could not be performed, since these 2 patients died subsequently. Following methanol poisoning, highest concentrations of formaldehyde have been found in the kidneys, liver and the gastro-intestinal tract. The gastritis associated with methanol intoxication may be severe and is occasionally hemorrhagic. Symptoms include anorexia, severe abdominal pain, vomiting, diarrhea, increased transaminases, or increased amylase. Other complications of severe methanol intoxication include oliguric renal failure, cardiac failure, and pulmonary edema (21, 22). Four patients in our study had high levels of ALT and AST. Two patients had high levels of amylase and creatinine.

Ethanol competes with methanol for the enzyme ADH in the liver, thereby preventing the accumulation of toxic metabolites of methanol in the body. The enzyme has a greater affinity for ethanol than it does for methanol. Therefore, in presence of ethanol, the metabolism of methanol to its toxic metabolites is greatly slowed. The target ethanol level is 100–150 mg/dL (23, 24). Dialysis is recommended in those patients who have visual disturbances, blood methanol of 50 mg% or more, have ingested more than 60 mL of methanol and have severe acidosis not corrected by sodium bicarbonate administration (25, 26). The patient must be followed closely after dialysis as a 'rebound' phenomenon has been well-documented, with the methanol levels increasing as much as 20 mg/dL over the 72 hour period following dialysis (23, 27).

Dialysis is very effective in the removal of both methanol and formic acid from the body. Hemodialysis is preferred over peritoneal dialysis because it offers a more rapid mechanism of clearance. Hemoperfusion should not be used because the columns may quickly become saturated with the methanol and then become ineffective (28, 29). In our study, HD was performed in 25 patients with complaints of blurred vision, blindness, or serious metabolic acidosis. Recurent metabolic acidosis developed in 3 patients after correction of metabolic acidosis (7, 10, and 19 hours after HD). A single HD of 7–8 hours duration was performed in 2 of the patients with recurrent metabolic acidosis and a 16 hour-HD was performed in the other patient. The patients were also given folic acid to promote catalase-mediated metabolism of formic acid. The serum Na, K, and P levels of the patients were monitored and replaced when necesary.

In the absence of serum methanol analyses, the osmolal gap is useful in assessing the indication for and duration of HD in methanol-poisoned patients. There is a good correlation between serum methanol and the osmolal gap during HD (16, 30). Some studies have confirmed the superiority of long-term HD for clearance of methanol. For our cases, HD was continued until correction of metabolic acidosis. Correction of metabolic acidosis by hemodialysis was achieved as early as 4 hours and at the latest, after 28 hours. During dialysis, blood samples were frequently collected and analyzed to determine acid–base status (31, 32)

In previous reports, the longest duration of HD, for 21 hours, has been performed in one patient because of severe methanol poisoning (33). We also had a patient under continuous control of blood gases and electrolytes, with 28 hours of HD treatment, who was eventually discharged. The overall mortality of methanol poisoning is approximately 19–46% and among the survivors the rate of permanent visual impairment is 20–25% (19). In Estonia, of the 154 patients admitted with suspected methanol poisoning, 68 (44%) died. The outcome was related to the degree of metabolic acidosis, serum methanol concentration, coma upon admission, and the patient's ability to hyperventilate. In 2 large series of patients with methanol poisoning reported in northern Europe, the mortality rates were 18% and 44%, respectively (7, 34, 35).

Seven (23.3%) of 30 patients with methanol intoxication in our study died. The patients died as early as 2 hours and after 34 hours, at the latest. All of these patients were unconscious at presentation and had metabolic acidosis with a high anionic gap. There was no relationship be-

tween hospital arrival time and the total duration of HD. The autopsy revealed differences in the levels of methanol, which may be due to the HD treatment and late autopsy. The remaining 21 patients (except for the 2 with permanent blindness and the 7 that died) were discharged from hospital after correction of metabolic acidosis and satisfactory creatine and amylase levels and liver function test results were observed.

Fomepizole, a competitive inhibitor of ADH, was approved recently as an antidote for methanol intoxication in adults. It acts in a similar fashion to ethanol. The clinical dose has not been established; however, 20 mg kg-1 day-1 was used in a small series. Ethanol increases inhibitory effects on ADH. Fomepizole is not available in Turkey and could, therefore, not be used in the treatment of our patients (36).

In conclusion, we found that unconsciousness and metabolic acidosis in cases of methanol intoxication were associated with an increased risk of mortality. The medical treatment and, if necessary, HD must be started as soon as possible, especially in the presence of mental state changes, visual disturbances, metabolic acidosis, and a history of methanol ingestion.

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