Risk factors related to poor outcome after methanol poisoning and the relation between outcome and antidotes – a multicenter study

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Introduction. Thorough prognostic and metabolic studies of methanol poisonings are scarce. Our aims were to evaluate the factors associated with sequelae and death from methanol poisoning, to develop a simple risk-assessment chart to evaluate factors associated with sequelae and death from methanol poisoning, and to compare the antidotes ethanol and fomepizole. Patients and methods. We present a retrospective observational case series of methanol-poisoned patients from Norway (1979 and 2002–2005), Estonia (2001) and Tunisia (2003/2004), and patients from two different centers in Iran (Teheran 2004–2009 and Mashhad 2009–2010) who were identified by a positive serum methanol and had a blood acid-base status drawn on admission. The patients were divided into different groups according to their outcome: Survived, survived with sequelae, and died. Results. A total of 320 patients were identified and 117 were excluded. Of the remaining 203 patients, 48 died, and 34 were discharged with neurological sequelae. A pH < 7.00 was found to be the strongest risk factor for poor outcome, along with coma (GCS < 8) and a PCO₂ ≥ 3.1 kPa in spite of a pH < 7.00. More patients died despite hyperventilation (low PCO₂) in the ethanol group. Conclusions. Low pH (pH < 7.00), coma (GCS < 8), and inadequate hyperventilation (PCO₂ ≥ 3.1 kPa in spite of a pH < 7.00) on admission were the strongest predictors of poor outcome after methanol poisoning. A simple flow-chart may help identify the patients associated with a poor outcome.

Keywords Methanol poisoning; Prognosis; Antidote; Metabolic disturbances

Introduction

Methanol poisonings are reported occasionally, typically in clusters.1–8 The clinical features (abdominal discomfort, dyspnea/hyperventilation, and visual disturbances) may mimic the signs and symptoms of other diseases, and many patients therefore die outside hospital before the diagnosis of methanol poisoning was made.1,4–7,9–11 Given the difficulty of obtaining the correct diagnosis – and the fact that methanol poisonings frequently occur in parts of the world where the availability of diagnostic equipment (serum-methanol- and osmolality analysis) is limited – the frequency of these poisonings is likely to be underestimated.

The mortality of methanol poisoning remains high; therefore, clinicians are searching for the proper tools with which to identify the patients with the highest risk of a poor outcome. There have been clusters of methanol poisonings for which both epidemiological and clinical parameters were reported.4–6,8,12 Most of these reports either cover smaller case series13–15 or lack laboratory parameters.1,11,16,17 To study the risk factors associated with poor outcome after methanol poisoning, we collected data from different areas where laboratory analyses and clinical features were available.5,13,14 We obtained a large comprehensive sample population for which blood analyses such as blood methanol and blood-gas were performed on admission. By combining patient samples from different poisoning clusters in different parts of the world, we hoped to diminish the influence of confounders (such as local variations of diagnostic equipment and treatment quality).
In this multicenter study, the main aim of our study was to (1) develop an easy-to-use prediction model for the outcome of methanol-poisoned patients. Secondary aims were to (2) determine whether the CNS-depressive effects of ethanol are related to outcome, and (3) to determine whether fomepizole is superior to ethanol in the treatment of methanol poisonings.

Patients and methods

Study design

The following observational case series were retrospectively collected from two different clusters of methanol poisonings in Norway (1979 and 2002–2005), one cluster in Estonia (2001), and one cluster in Tunisia (2003/2004). Additional data were obtained from two centers in Iran (Logham-Hakim Hospital for 2004–2009 and Mashhad University Hospital for 2009–2010). The various authors took part in the diagnostic procedures and the treatment, and the patients were thereafter collected from the emergency department logs and charts.

The study was designed as a retrospective observational case series study with the following inclusion criteria: (1) Patients admitted to hospital alive with a diagnosis of methanol poisoning for which the diagnosis was made on admission or later verified by a positive serum-methanol analysis; (2) Blood-gas analysis was performed at the time of admission. All patients who were administered any treatment before admission that could potentially interfere with the analysis (including mechanical ventilation, buffer or antidote) were excluded from the study. A few patients were intubated to secure their airways before admission, yet not mechanically ventilated – these were not excluded. Many of the patients included in this study have been included in studies that were previously published separately in a different context, but these patients have never been analyzed as a group and never analyzed with the aims of the present study.

Data collection

On admission (before any treatment was given), the following data were recorded: state of consciousness (coma defined as GCS < 8 – recorded in the chart as “coma” or a numeric GCS), serum-methanol (not necessarily drawn on admission, but verified as positive in all included patients), pH, pCO₂, base deficit (BD), HCO₃⁻, serum-potassium (serum-K), and serum-creatinine. All the patients from Estonia were evaluated for their consciousness after 1 hour in addition to the original evaluation (the other parameters were only measured once): “Awake”: The patients who stayed awake after initiation of ethanol treatment, “Awake-coma”: The patients who were admitted awake, but lost their consciousness after the initiation of ethanol treatment, and “Coma”: The patients who were unconscious already on admission. The outcome was defined as the status at discharge from the hospital. To evaluate both mortality and morbidity (defined as discharged with sequelae – see below), the patients were divided into three groups: (1,2) Group I: survivors without sequelae; Group II: survivors with sequelae (visual disturbances or brain damage on discharge); and Group III: the patients who died.

Laboratory methods

The methanol concentrations were measured with different instruments. A Pye Unicam Model 104 gas chromatograph equipped with a single flame ionization detector was used in Norway in 1979, and a gas chromatography system with a flame ionization detector and a headspace injector (Fisons GC 8000; Rodano, Italy) (sensitivity 1.3 mmol/L and day-to-day coefficient of variation 5%) was used in 2002–2005. A UV-Vis spectrophotometer (Spectronic-20D; Milton Roy, Belgium) operated at a wavelength of 570 nm was used in Iran, and a gas chromatography system with a headspace injector (Hewlett Packard 4890D chromatograph and HP 7694E headspace sampler) and a flame ionization detector (GC-FID) was used in Estonia. In Tunisia, the methanol concentrations were measured using two different methods: the CORDEBARD enzymatic method (oxydo-reduction) using an Integra 400 system (coefficient of variation = 4.2%) and a novel gas chromatography technique using a Shimadzu instrument with a manual injector.

Statistical analyses

Statistics were performed using SPSS version 19.0. Regarding the associations between the different blood-gas parameters/serum-K and serum-creatinine vs. outcome, the data were considered sufficiently close to the normal distribution to be compared with one-way Anova with Bonferroni correction for pairwise group comparison (Table 1).

We used a multivariate logistic regression analysis to identify the factors which may be used to look for variables associated with a poor outcome (in statistical terms a decision tree). In this analysis, death was the dependent variable, whereas a selection of other variables such as coma, pH, pCO₂, HCO₃⁻, base deficit, serum-potassium, and creatinine was used as independent variables. Methanol was not evaluated as some of the methanol analyzes were not drawn on admission (but they were all positive). Afterwards, a backwards variable selection was performed until all remaining variables were significant (p < 0.05) (Table 2).

To further confirm the associations between the different parameters and death, we performed a Receiver-Operated Characteristic (ROC) curve test, where the area under the ROC curve was used as a measure of the strength of the association between the continuous parameters and mortality. Threshold values, odds ratio (OR), and 95% confidence intervals (CI) are presented in Table 3.

Independent T-tests were used to compare means in different outcome groups where the groups were sufficiently large.

The risk assessment chart was created by initially separating the patients according to their state of consciousness: coma (GCS < 8) – yes/no. With the use of a ROC-curve, the two groups were then separated based on
Table 1. The different outcome groups among the patients as related to different admission parameters.

<table>
<thead>
<tr>
<th></th>
<th>Group I* (n = 121)</th>
<th>Group II* (n = 34)</th>
<th>Group III* (n = 48)</th>
<th>Overall p (ANOVA)</th>
<th>Overall p (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (♂:♀)</td>
<td>99:22</td>
<td>27:7</td>
<td>34:14</td>
<td>160:43</td>
<td>–</td>
</tr>
<tr>
<td>Age (years) Median (range)</td>
<td>44 (3–77)</td>
<td>42 (17–65)</td>
<td>42 (15–65)</td>
<td>44 (3–77)</td>
<td>–</td>
</tr>
<tr>
<td>Coma (GCS &lt; 8) on admission n (%)***</td>
<td>8 (6.6%)</td>
<td>11 (32.4%)</td>
<td>41 (85.4%)</td>
<td>60 (30.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Serum-methanol (mmol/L)**** Median (range)</td>
<td>31 (1–179)</td>
<td>65 (18–158)</td>
<td>59 (8–199)</td>
<td>45 (1–199)</td>
<td>–</td>
</tr>
<tr>
<td>pH Median (range)</td>
<td>7.24 (6.52–7.57)</td>
<td>7.15 (6.60–7.46)</td>
<td>7.16 (6.34–7.57)</td>
<td>p &lt; 0.001</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>pCO₂ (kPa) Median (range)</td>
<td>3.2 (1.0–7.5)</td>
<td>2.9 (1.2–6.8)</td>
<td>3.4 (1.0–15.9)</td>
<td>p &lt; 0.001</td>
<td>ns</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L) Median (range)</td>
<td>10 (2.0–37.8)</td>
<td>7 (1.0–26.0)</td>
<td>6.2 (1.0–37.8)</td>
<td>p &lt; 0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>Base deficit (mmol/L) Median (range)</td>
<td>17 (−3–30)</td>
<td>23 (−2–41)</td>
<td>21 (−3–42)</td>
<td>p &lt; 0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum-K (mmol/L) Median (range)</td>
<td>4.3 (2.6–7.7)</td>
<td>4.2 (3.7–8.1)</td>
<td>4.6 (2.6–8.1)</td>
<td>p &lt; 0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum-creatinine (μmol/L) Median (range)</td>
<td>79 (35–212)</td>
<td>99 (40–186)</td>
<td>89 (35–380)</td>
<td>p &lt; 0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidote (F = fomepizole  E = ethanol)</td>
<td>F: 22 (18%)</td>
<td>F: 4 (12%)</td>
<td>F: 6 (13%)</td>
<td>F: 32 (16%)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>E: 99 (82%)</td>
<td>E: 30 (88%)</td>
<td>E: 42 (87%)</td>
<td>E: 171 (84%)</td>
<td>–</td>
</tr>
</tbody>
</table>

ns = not significant.
Conversion factors:
mg/dL to mmol/dL (methanol): 1:3.2.
mmHg to kPa (pCO₂) = 7.51.
mmol/L to mmol/L (HCO₃⁻, BD, K⁺) = 1:1.
mg/dL to mol/L (creatinine) = 1:88.4.

*Group I = Survivors without sequelae, Group II = Survivors with sequelae, Group III = Patients who died.
**Bonferroni correction.
***One unknown state of consciousness in each group. Statistical method: Chi square.
****Significance not presented for methanol as some of the samples were drawn later in the course.

Table 2. The results of the multivariate analysis on the factors associated with a poor outcome.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>OR</th>
<th>95% confidence interval (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma yes vs. no</td>
<td>10.2</td>
<td>3.3–32.0</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>pH 0.1 unit increase</td>
<td>0.58</td>
<td>0.46–0.75</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Clinical interpretation: If the pH is increased by 0.1 units, the odds for poor outcome is reduced by 42%.

The pH with the highest combined sensitivity and specificity with respect to separate the survivors from the patients who died. Then, the high-risk group (pH < 7.00) was split in two groups based on the median, with the following assessment then based on three different pH groups. Finally, the patients in a coma with a pH value between 6.74 and 6.99 were evaluated for their ability to hyperventilate (defined by a low pCO₂). This threshold pCO₂ value was estimated using the ROC curve to obtain the highest possible combined sensitivity and specificity. Fisher’s Exact Test was used when analyzing contingency tables with small sample sizes.

To evaluate the possible interference with ethanol on the patients’ consciousness and relate it to their outcome, the patients from the Estonian outbreak were studied: Their consciousness was also registered 1 hour after the initial admission (after ethanol treatment) upon where their pH and pCO₂ (degree of hyperventilation) from the admission parameters were compared towards the different outcome groups.

Results

Patient characteristics and outcomes

Among the 320 patients, 219 were identified as positive for serum-methanol at the time of analysis (Fig. 1). Sixteen patients who were treated prior to admission with a buffer,
an antidote or mechanical ventilation were excluded from the statistical analyses, leaving 203 patients verified as positive for serum-methanol who had not undergone any treatment prior to admission.

The admission characteristics are shown in Table 1.

**Analysis of poor outcome**

A combination of multiple regression analysis and the ROC-curve identified pH and coma to be the strongest prognostic factors along with the patients’ ability to lower their pCO₂ when being acidic. When performing the multivariate analysis, only pH and coma remained significant (Table 2). This procedure was repeated in patients with coma and pH > 6.74 and pH < 7.00. Then only one variable remained in the model: pCO₂.

The prognostic markers along with their thresholds, odds ratio (OR) and the 95% confidence intervals (95% CI) are presented in Table 3.

HCO₃⁻, BD, serum-K and creatinine were significantly associated with poor outcome, but they were dependent on pH, and thus the significance disappeared when corrected for pH by regression analysis.

A risk-assessment flow-chart and the corresponding outcome based on the three most important clinical features are shown in Fig. 2.

Among the survivors, there was a trend toward decreased pCO₂ at lower pH values. An opposite trend was found among the patients who died. The spread in ventilation among the survivors was high (represented by a low R² = 0.097), but the difference between the groups was highly significant (p < 0.001) (Fig. 3).

**Use of antidotes**

The patients were separated into two groups based on the antidote used; fomepizole was the antidote of choice for 32 of the patients (Norway 2002–2005), and for the remaining 171, only ethanol was used. There was a trend toward a “positive” leftward shift in morbidity and mortality (i.e., a better outcome) in the fomepizole group relative to the ethanol group regarding the pH, but this difference was not significant (Fig. 4A). Further, there was a trend toward hyperkalemia in the poor-outcome fomepizole groups (Group II and III), whereas many of the surviving patients treated with ethanol suffered from sequelae despite having a normal serum-K (not significant, Fig. 4B). Finally, patients in the ethanol group seemed to die significantly more often despite (spontaneous) hyperventilation relative to patients in the fomepizole group (p = 0.034) (Fig. 4C).

**Ethanol and level of consciousness**

Among the patients treated for methanol poisoning in Estonia, 25/64 (39%) of the patients who were awake on admission fell into a coma associated with the use of ethanol as an antidote. None of the patients in the first group (“awake”) died, whereas six (24%) in the latter group died (p = 0.005, Fisher’s Exact Test). The “awake-coma” group seemed to be more acidic than the “awake” group (p = 0.005 in Group 1), and the “coma” group seemed to be more acidic than the “awake-coma” group (p = 0.001 in Group 3) as illustrated in Fig. 5A (too low number of patients to compare statistically in Group 2). It also appeared that the patients in the “awake-coma” group died despite lower pCO₂ values (p = 0.019 in Group 3) (Fig. 5B). All patients admitted in the...
Prognosis in methanol poisoning vs. antidote

Discussion

Prognostic parameters

There was a trend toward increased morbidity and mortality with increasing degree of metabolic acidosis, as observed previously. When ranking the parameters according to their ability to predict outcome, pH ranked as the most important parameter, followed by coma on admission and pCO₂ vs. pH (i.e., the ability to compensate for metabolic acidosis by hyperventilation). A high base deficit (BD), reflecting acidosis, was also clearly associated with a poor outcome, but its significance was not independent of the pH. This result is not surprising because base deficit reflects, by definition, solely the metabolic components of the acidosis.

Further, there were significant differences among the groups with respect to HCO₃⁻ (all groups) and pCO₂ (Gr I vs. Gr II and Gr II vs. Gr III), although neither difference was independent of pH. These differences have not been reported with statistical significance in the literature. There are two likely reasons for this discrepancy: Our study included a large number of patients, giving more power to the analysis, and except for four poisoning clusters in previous studies, the patients were usually not separated into three different groups based on outcome to evaluate both the morbidity and the mortality. Combining all survivors (only separated into two groups) is likely to bias the results. Regarding serum-K, there were significant differences between Groups I-II and Groups II-III, but these differences were also dependent on pH. In addition, there seemed to be higher levels of creatinine among the patients who died, probably reflecting compromised circulation. The OR for mortality in Table 3 supports this theory.
hyperventilation, such ventilation may cause a fatal worsening of the acidosis.

Ethanol vs. fomepizole

The morbidity and mortality associated with methanol poisoning depend on the time from methanol intake to the initiation of treatment, the amount of formic acid produced, and the degree of metabolic acidosis. It is therefore not possible to compare the outcomes from the two antidotes directly in retrospective studies. However, it is possible to compare these outcomes indirectly using the admission parameters (where these factors would already be acknowledged), given similar treatments in the two groups.

In spite of the size of our patient sample, there were a limited number of patients in the fomepizole group, especially with regard to the number of fatalities. Ethanol is an efficient antidote when given at an optimal dose, and it is likely that a prospective approach involving a larger number of patients in all groups will be necessary to reveal significant differences in outcome based on the hard end-points (morbidity and mortality). However, the present study does suggest a trend toward a leftward shift in morbidity and mortality (i.e., better outcome), as shown in Fig. 4A. In spite of the severe metabolic acidosis reflected by low pH, more patients who were administered fomepizole survived with sequelae instead of dying compared with patients with a similar pH treated with ethanol. However, because of the limited number of patients in the fomepizole group, the analysis was more susceptible to the effects of outliers, such as one of the patients in the fomepizole group III who died despite having a pH of 7.13 on admission. The diagnosis of this patient was delayed, and treatment was not initiated until 6 hours after admission, at which time the patient was already much more acidotic (pH 6.8) and in a coma. Without this one outlier, the difference between the two antidote groups would be significant (p = 0.038). The serum-K, which also reflects the level of

The risk-assessment chart

The easy-to-use risk-assessment flow-chart and a corresponding score can prove helpful when triaging patients in larger outbreaks with many victims in a short time-span. It can also be used as a simple assessment to predict the patient’s outcome already on admission solely based on standard data. The obvious benefits for patients hyperventilating (see risk group D vs. E, Fig. 2), as well as the protective effect of staying awake (see risk group C vs. F, Fig. 2), calls for a focused and aggressive start of treatment in these patients (see also below).

The importance of a lack of respiratory compensation with respect to the outcome of patients with metabolic acidosis was first reported after the cluster of poisonings in Norway in 2002–2005 and was later confirmed in the Estonian outbreak and in an Iranian study. When analyzing all of the available data in the present study (Fig. 3), this parameter again seemed to separate the survivors from the patients who died with a highly significant trend, allowing the prediction of the outcome of the patient at the time of admission – provided that adequate treatment is given. The fact that the survivors seem to have a large variation in their ventilation (R² = 0.097) is not at all surprising, as most of them have a mild to moderate acidosis, and so they have a limited need for hyperventilating. The role of hyperventilation in patient prognosis is supported by a significant number of the patients in Estonia being admitted awake (n = 64) but falling into a coma after the initiation of ethanol therapy (CNS-depression) (n = 25/64; 39%) (see below). Assessing the ability of patients with a metabolic acidosis to hyperventilate will not only provide evidence of the importance of this new prognostic feature, but will also highlight the importance of avoiding normoventilation in these patients after they are put on a ventilator. This situation is challenging, with the patient’s condition calling for intubation and sedation, which inhibits the physiological respiratory drive. If ventilatory support is not sufficient to provide

Fig. 3. The association between pH and serum pCO₂ as a prognostic factor. The dotted line = the trend line of the survivors. The solid line = the trend line of the dead.
indicating that the patients in the fomepizole group had a higher survival rate if they were able to hyperventilate.

The CNS-depressive effects of ethanol

None of the above results demonstrate that fomepizole is superior to ethanol given optimal treatment, but providing optimal treatment seems to be one of the major problems with ethanol, as it is difficult to maintain a continuous serum-level of 100 mg/dL.21,22 Our data also indicate that the CNS-depressive effect of ethanol may interfere with treatment and the need for mechanical ventilation and may influence the outcome: None of these patients from the Estonian cluster were treated with mechanical ventilation before admission, thus their respiratory status changed after the initiation of ethanol. The patients who became comatose after treatment with ethanol seemed to have a poorer outcome than the patients who stayed awake (6/25 (24%) vs. 0/39 patients died). These patients who lost their consciousness seemed to have a severity of metabolic acidosis between that of the patients who were awake and the patients who were in coma in all outcome groups, suggesting that they are more susceptible to falling into a coma with ethanol treatment the more severely poisoned they are (Fig. 5A). Further, they seemed to die in spite of a higher degree of hyperventilation on admission (Fig. 5B), reflecting the fact that the removal of their “drive” after the addition of a CNS depressant may be associated with a poorer outcome. The fact that these patients were all part of the same cluster decreases the influence of bias due to different qualities of treatment being available for the different patients. The above findings suggesting CNS depression affects outcome is supported by the data found by Hassanian-Moghaddan et al. where co-ingestions with opioids were associated with a poorer outcome.13

Strengths and limitations

The results shown above are attributed to different confounders, most importantly being retrospective data with its limitations: Addressing the link between the ability to hyperventilate when being severely acidotic to be associated with a better outcome should ideally have been confirmed in a prospective randomized trial. However, this is based on some well-established medical theories: 1. The more hyperventilation, the better correction of a metabolic acidosis, and 2. Acknowledging ethanol as a CNS depressant. Addressing the respiratory drive vs. outcome, the consciousness vs. outcome and the CNS-depressive role of ethanol in this sense thus seems adequate in the largest methanol-poisoning material available until now.

An additional limitation is the possible variations in the time from intake to the start of treatment, and the available modalities for treatment (other than the antidote). However, a delay in treatment was found in both groups (although the one outlier in the fomepizole group having much more impact because of the smaller number of patients), and the same treatment modalities were found in all of the countries included in this study (including buffer and hemodialysis).

Fig. 4. Outcome by group – fomepizole vs. ethanol. Group 1 = Survivors without sequelae, Group 2 = Survivors with sequelae, Group 3 = The patients who died. The symbols “x” and “O” are outliers. Group 2: Too small to compare statistically. (A) pH vs. outcome group. (B) Serum-K vs. outcome group. (C) pCO₂ vs. outcome group. Significant difference in Group 3 (p = 0.034) (see colour version of this figure online at www.informahealthcare.com/ctx).

acidosis, shows a clear trend toward survival in the fomepizole group if serum-K was within the normal range (<5 mmol/L) (Fig. 4B). There were significantly lower pCO₂ values among the patients who died in the ethanol antidote group (Fig. 4C),
Some of the calculations were based on smaller groups, but this was accounted for by using Fischer Exact Test to make it statistically valid. Still, there is an increased risk of biases in calculations of smaller groups. The fomepizole group (only used on one site) was limited in number, especially for patients discharged with sequelae or patients who died. This limited sample size gave an insufficient power to allow the statistical analysis to find differences with respect to outcome in this retrospective study.

Conclusion

pH is the strongest prognostic marker in methanol poisoning. Being awake on admission and being able to hyperventilate seem to be related to a better outcome. A simple flow-chart can help identify those patients who are at risk of a poor outcome. There seems to be a trend toward a positive “leftward shift” in morbidity and mortality (i.e., better outcome) when using fomepizole as an antidote, but a definite conclusion would require a prospective approach and preferably a larger fomepizole group. Using ethanol as an antidote has the potential to increase the risk of death unless the CNS-depressive effects are compensated for by mechanical hyperventilation.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References