Saudi Pharmaceutical Journal 32 (2024) 102018

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Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Methanol intoxication in the central region of Saudi Arabia: Five case studies

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ARTICLE INFO

Keywords:
Methanol
Ethanol
Postmortem
Poisoning
Vitreous humour
Blood

ABSTRACT

Outbreaks of methanol poisoning have been described in the medical literature worldwide. However, the few outbreaks that have occurred in Saudi Arabia remain undocumented. This is especially noteworthy in light of the fact that Saudi Arabia is among the countries that explicitly prohibit the usage of alcoholic beverages and recreational drugs. Herein, we describe five cases of methanol poisoning in Saudi Arabia. The first three comprise patients admitted to the emergency room (ER) with signs of methanol toxicity, such as heart palpitations, vomiting, and blurred vision; otherwise, those patients were considered medically free. The remaining two cases were examined postmortem. A headspace gas chromatography-flame ionization detector was used to test blood, vitreous humor, and urine samples for methanol. Specific lethal concentrations of methanol were defined based on published case studies as 23–740 mg/dL in blood and 12–396 mg/dL in vitreous humor. In postmortem cases of our present study, samples exhibited lethal concentrations: 118 and 257 mg/dL in blood, 116.3 and 283 mg/dL in vitreous humor. In ER cases, methanol concentrations in urine samples were lower, at 7.5, 9.1, and 20.9 mg/dL; however, toxic symptoms were still observed. These case studies indicate that it is necessary to raise community awareness about the risk of methanol poisoning in order to minimize future poisoning epidemics.

1. Introduction

Alcohol is widely used in Western cultures and is frequently incorporated in celebrations and events. Conversely, it is not widely consumed in Arab countries and is even prohibited in the Kingdom of Saudi Arabia due to the culture and Islamic faith of these countries (Alhaidan et al., 2022). In Islamic countries, regulations prohibiting drinking of alcohol have inadvertently led to increased alcohol consumption from the black market. This black-market alcohol is more likely to be contaminated with substances such as methanol (Levine and Kerrigan, 1999, Alhaidan et al., 2022). A severe medical conundrum is thus created by the patients' delayed hospital presentation, delayed case identification, and non-specific clinical symptoms at the time of admission, especially in the absence of a clinical or forensic toxicologist. Additionally, the social stigma associated with alcohol consumption can strongly impact willingness to present a child or family member at the hospital, which delays identification and affects epidemological and statistical data concerning methanol poisoning (Eskandrani et al., 2022).

Methanol, also known as methyl alcohol, usage is particularly dangerous due to its high toxicity. Considering the similarity in taste and smell between methanol and ethanol, (Barceloux et al., 2002, Galvez-Ruiz et al., 2015), Local manufacturers sometimes substitute methanol for ethanol during manufacturing; or locally manufactured alcohol can sometimes be contaminated by methanol, and both can be happened due to poor quality control procedures. Local alcohol manufacturers sometimes substitute methanol for ethanol to increase production volume and

Peer review under responsibility of King Saud University.
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https://doi.org/10.1016/j.jsps.2024.102018

Available online 5 March 2024

profit margins (Doreen et al., 2020, Tian et al., 2022, Alqurashi et al., 2023). This has resulted in numerous cases of methanol poisoning (Sharma et al., 2012, Galvez-Ruiz et al., 2015, Zamani et al., 2019, Doreen et al., 2020).

Within the body, methanol undergoes negligible renal excretion, but can be eliminated unchanged via exhalation. It also undergoes oxidation in the liver to produce primordial formaldehyde, which is then further oxidized alongside conversion of NAD + to NADH, producing formic acid (Waters et al., 2018, Doreen et al., 2020). This metabolism of methanol into formic acid is the primary cause of methanol poisoning. The two main enzymes responsible for methanol oxidation are alcohol dehydrogenase and then aldehyde dehydrogenase (Nekoukar et al., 2021; Alqurashi et al., 2023).

Methanol poisoning can lead to gastrointestinal problems such as nausea, vomiting, and abdominal pain. It also results in central nervous system (CNS) suppression, which manifests as disorientation and drowsiness within 0.5–4 h post-ingestion. Decompensated metabolic acidosis, accompanied by blurred vision, photophobia, diplopia, early or late-onset blindness, and less frequently nystagmus, may develop after a latent period of 6–24 h, depending on the absorbed dose. Blurred vision in the context of full mental awareness is a strong indicator of methanol poisoning (Galvez-Ruiz et al., 2015, Çetinkaya et al., 2021, Nekoukar et al., 2021, Tian et al., 2022, Almoallem, 2023).

A lethal dose of 40 % methanol is typically 30 ml, while a 10 ml volume can cause blindness. Upon absorption into the body, methanol distributes throughout the body's water content, which comprises a volume of 0.77 L/kg. The distribution half-life of methanol is about 8 min, longer than its absorption half-life. As a result, peak serum concentrations are achieved relatively quickly after ingestion, and then decline thereafter (Galvez-Ruiz et al., 2015, Nekoukar et al., 2021). The majority of fatalities occur within 48 h from the time of contaminated alcohol consumption, with the shorter lethal timeframe being approximately half a day (Chng et al., 2020). *Molina and Hargrove* previously published case studies of methanol deaths, and found that methanol is tolerated at blood concentration of 0.15–3 mg/dL, but toxic at concentrations of 20–130 mg/dL (Molina and Hargrove, 2019). Moreover, Molina and Hargrove reported tissue-specific lethal concentrations of methanol, namely 23–740 mg/dL in the blood and 12–396 mg/dL in the vitreous humor (Molina and Hargrove, 2019). In regard to ethanol, it was determined that ethanol concentrations was ranged from 12 to 599 mg/dL in the vitreous humor of postmortem cases (De Martinis et al., 2006).

It is well-established that microorganisms can generate alcohol postmortem, which can confound determinations of ethanol concentration, particularly when there is a significant time gap between death and analysis (Alsayed et al., 2022). Blood samples may present a particular challenge as ethanol can form within days at room temperature (Levine and Kerrigan, 1999). Consequently, it is advisable to assess ethanol concentration in a variety of sample types, including urine, vitreous humor (VH), and blood from different body sites. VH specimens are typically free of glucose, and hence are less prone to postmortem alcohol production; VH is therefore a valuable specimen for ethanol testing when blood is unavailable, and especially in postmortem criminal toxicology. In patients at the hospital, urine samples typically present with a higher positive value than blood samples, because ethanol is metabolized more slowly in urine. Delayed arrival at the hospital and non-specific clinical symptoms at the time of admission create opportunity for further methanol metabolism (Jones, 2006, Alsayed et al., 2022).

The present research focuses on understanding and studying cases of methanol poisoning. Its scope consists of five cases: three cases of methanol poisoning admitted to the ER and two postmortem cases due to unintentional oral ingestion in beverages.

2. Case presentation

2.1. Emergency room (ER) cases

The ER cases (1, 2, and 3) involved patients who presented to the Security Forces Hospital (SFH), Riyadh, Kingdom of Saudi Arabia with symptoms of methanol toxicity, including vomiting, heart palpitations, and blurred vision; they were medically free otherwise. Blood and urine samples were analyzed for methanol using a headspace gas chromatography-flame ionization detector (HS-GC-FID). The cases were evaluated, symptoms confirmed, and examinations conducted by specialist physicians. Tests for methanol poisoning were ordered given the patients' medical history and symptoms. The types of samples taken from patients were determined based on time considerations, along with the information provided by the patients themselves. All three patients were accepted for hemodialysis treatment, as fomepizole was not available. Subsequent care involved follow-up for potential kidney and endocrine diseases.

2.2. Postmortem cases

The postmortem cases (4 and 5) were considered criminal due to methanol poisoning. The postmortem samples were investigated in the Poisons Control & Medical Forensic Chemistry Center, Riyadh, Saudi Arabia. Femoral blood, urine, and VH samples were analyzed for methanol and ethanol using HS-GC-FID. Case 4 involved a 29-year-old man, 166 cm tall and weighing 60 kg. The deceased was brought to the hospital, and the cause of death was suspected to be methanol poisoning. The body was not in a state of putrefaction. The estimated time of death was around 12 noon on 5/15/2021 CE. There was no information available about other toxic substances. On 05/19/2021, femoral blood and vitreous samples were collected at 12:55p.m., and a urine sample was collected at 12:56 pm. Case 5 involved a 37-year-old man, measuring 186 cm in height and 86 kg in weight. He was found deceased with a substance resembling intoxicants near him. The body showed minimal signs of decomposition. The time of death was estimated at 12 noon on 5/16/2021 CE. No information was available about specific toxic substances. Femoral blood samples were collected on 05/19/2021 at 12:46 pm. Urine and vitreous humor samples were collected one minute later, at 12:47 pm.

3. Materials and methods

3.1. Consumables/chemicals

All chemicals were of analytical gas chromatographic reagent grade. Standard solutions of ethanol, methanol (Chem-Lab, LC-MS grade, 2.5 L; made in Belgium), isopropyl alcohol (IPA) (LiChrosolv mERCK, LC-MS grade, 2.5 L; made in Germany), and acetone (Laboratory Chemical-Atlas Medical, LC-MS grade, 2.5 L; made in the UK). were prepared using deionized water (18 MΩ cm), which was obtained from a Milli-Q water purification system (ELGA VEOLIA – PureLab-flex, 18.5 L; made in the UK). High purity helium, hydrogen, and dried air gases (for gas chromatography) were purchased from Abdullah Hashim Industrial Gases & Equioment Co.Ltd., Riyadh, Saudi Arabia.

3.2. HS-GC-FID conditions

All analyses were performed on a Static and Dynamic Headspace System - HT3 passing through a SCION GC-436 system. The chromatograph was supplied with a single injection attached to a column (SCION-WAXMS, 30 m, 0.25 mm ID, 0.50 mm film thickness, The Netherlands or UK) and a FID, and operated under three gas conditions: zero air, helium, and hydrogen with purity of 99.999 % (Table 1).

Table 1
Headspace System - HT3 and GC-FID Conditions.

Name of the Parameter	Set Point
Mass Flow Rate	50.0 ml/min
Pressure	0.0 psig
Transfer temperature	120 °C
Oven temperature for the system	105 °C
Platen temperature	70 °C
Injector temperature	125 °C
Oven temperature for the detector	45 °C
Detector temperature	200 °C
Stabilization time	30 min

3.3. Method validation of methanol and ethanol

The precision, sensitivity, specificity, linearity and accuracy were determined for method validation (Table 2). Analytical precision was determined using relative standard deviation (RSD) calculations, for which the procedure was repeated eight times for each concentration on each of five consecutive days. Linearity was assessed by analyzing 20 separate calibration curves on five consecutive days. The accuracy of each point was determined, and should not exceed 20 %. Linearity was demonstrated by R2 values, which were consistently higher than 0.999. Accuracy was determined by repeating the procedure eight times for each concentration over five consecutive days. The LOD and LOQ values of our methodology for detecting methanol or ethanol in ER patient samples were found to be 1 mg/dL and 5 mg/dL, respectively. Notably, postmortem redistribution can affect determinations in postmortem biological samples. However, all data obtained are reported.

4. Results and discussion

This study evaluated five cases of methanol poisoning in the Kingdom of Saudi Arabia that occurred during the outbreak in the second quarter of 2021. All cases involved middle-aged males, and were divided into two groups: patients admitted to the ER, and individuals who had died due to methanol poisoning. A representative chromatogram of methanol in a urine sample is illustrated in Fig. 1, and a chromatogram for the limit of quantification (LOQ) of headspace gas chromatography is shown in Fig. 2.

Table 2
Method validation summary for ER patients.

Parameter	Methanol	Ethanol
Analytical precision	Within-run %RSD = 9.35 % (10 mg/dL) Within-run %RSD = 6.89 % (40 mg/dL) Within-run %RSD = 7.99 % (150 mg/dL) Between-run %RSD = 14.82 % (10 mg/dL) Between-run %RSD = 6.98 % (40 mg/dL) Between-run %RSD = 7.89 % (150 mg/dL)	Within-run %RSD = 2.16 % (10 mg/dL) Within-run %RSD = 3.03 % (40 mg/dL) Within-run %RSD = 4.51 % (150 mg/dL) Between-run %RSD = 4.39 % (10 mg/dL) Between-run %RSD = 3.48 % (40 mg/dL) Between-run %RSD = 4.61 % (150 mg/dL)
Analytical sensitivity (detection limit)	Signal to noise ratio (3 times the noise ratio) = at least 1 mg/dL Note: The cut off = 10 mg/dL.	Signal to noise ratio (3 times the noise ratio) = at least 1 mg/dL Note: The cut off = 10 mg/dL.
Analytical specificity (interferences)	No interferences were seen	No interferences were seen
Linearity	R^2 was always higher than 0.999 in the range of the lower limit of quantification (LLOQ) (at least 5 mg/dL)	R^2 was always higher than 0.999 in the range of the lower limit of quantification (LLOQ) (at least 5 mg/dL)
Accuracy (method comparison)	10 mg/dL = 107.3 % 40 mg/dL = 108.5 % 150 mg/dL = 108.9 % (Acceptable range between 80 and 120 %)	10 mg/dL = 111.2 % 40 mg/dL = 106.3 % 150 mg/dL = 106.1 % (Acceptable range between 80 and 120 %)
Reportable range	Above 10 mg/dL will be considered Positive.	Above 10 mg/dL will be considered Positive.

The complex relationship between blood methanol concentration and clinical consequences may make interpreting methanol consumption challenging. Factors that affect detected methanol concentrations and should be considered include chronic ethanol intake, sample timing, and individual variability. For instance, in ER3rd case, methanol was found in the urine but not in the blood. This might be because the blood samples were collected after completion of methanol metabolism, which reduced its concentration to below the limit of detection. The details of the results of methanol and ethanol detection are given below in Table 3 and Table 4, respectively.

The ER cases in this study exhibited methanol concentrations ranging from 7.5 to 20 mg/dL, which were accompanied by a range of clinical symptoms indicative of methanol toxicity, including nausea, vomiting, abdominal pain, tachycardia, and blurred vision. Case 3 notably had a significantly higher concentration of methanol, at 20.92 mg/dL, than did Cases 1 and 2, which were below 10 mg/dL. However, all three cases had generally similar symptoms despite the differing concentrations of methanol. Interestingly, Case 3 also featured a high ethanol concentration of 22.72 mg/dL, which helped to inhibit methanol metabolism and reduced the associated toxicity (Eskandrani et al., 2022). However, we did not detect ethanol in the urine of Cases 1 and 2, suggesting the completion of ethanol excretion before sample collection.

In postmortem cases, it is essential to obtain a VH sample to ensure that the observed methanol concentration is not attributable to natural processes but rather owes solely to alcohol ingestion (Alsayed et al., 2022, Eskandrani et al., 2022). In both Cases 4 and 5, the blood methanol concentrations exceeded 100 mg/dL. The lethal blood concentration of methanol ranges from 23 to 740 mg/dL. In Case 4, the high concentration of methanol was attributable to alcohol adulteration. For Case 5, the deceased exhibited a slight degree of putrefaction, and therefore extra care was taken to obtain a vitreous fluid sample. Ultimately, the primary cause of death for both was determined to be the high methanol dose.

All incidents examined in this study occurred within the same period in 2021. This may suggest that all patients obtained alcohol from the same source or jointly attended a social gathering where alcohol was served. The typical scenario for methanol poisoning involves symptom development within two days of ingestion (Chng et al., 2020), but for social and religious reasons, patients often hesitate to report symptoms or disclose the actual cause. It is worth noting that we were unable to determine the source of the alcohol consumed prior to methanol poisoning in all cases. This implies that the victims most likely consumed a counterfeit alcoholic drink containing methanol, either mixed with a percentage of ethanol or consisting solely of methanol.

5. Conclusion

Black markets, often controlled by covert networks, are common venues for the promotion and sale of locally-produced alcoholic beverages in Saudi Arabia. Therefore, it is crucial to develop monitoring protocols, heighten awareness among health organizations, and emphasize the importance of measuring ethanol and methanol levels in those products. Clinical and analytical toxicologists should play a crucial role in the management of methanol poisoning situations. Greater attention to and international awareness of epidemics of methanol poisoning is needed, and it is strongly advised that diagnostic and treatment protocols be updated on a regular basis using evidence-based methodology.

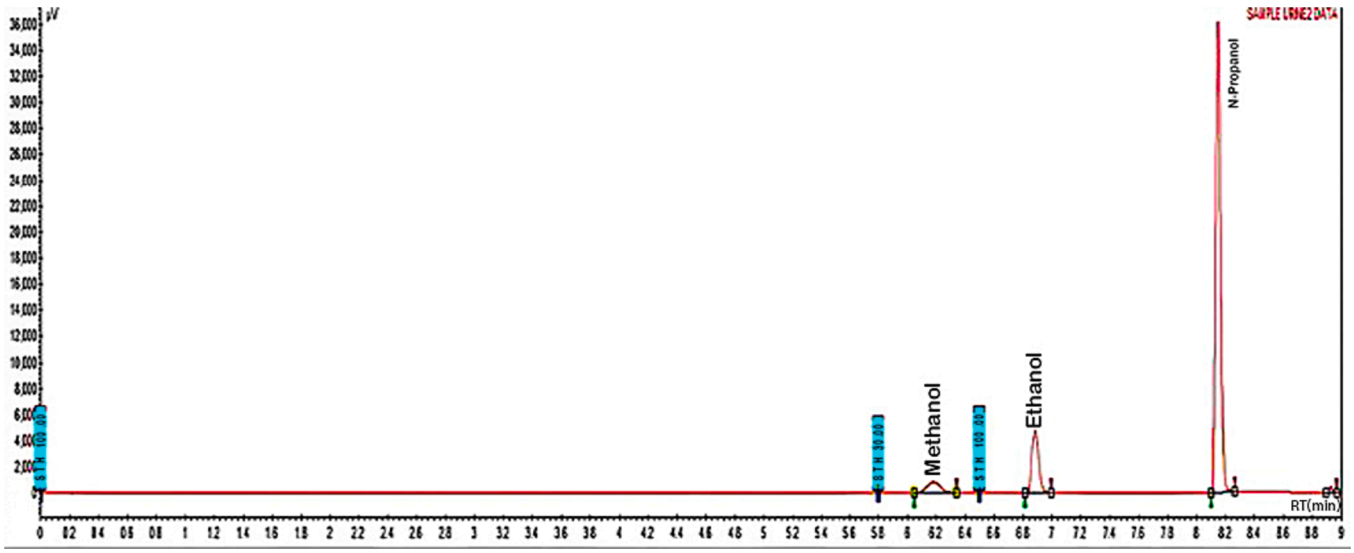

Fig. 1. Representative chromatogram of methanol and ethanol in urine sample (from Case 3, ER). The internal standard is n-propanol.

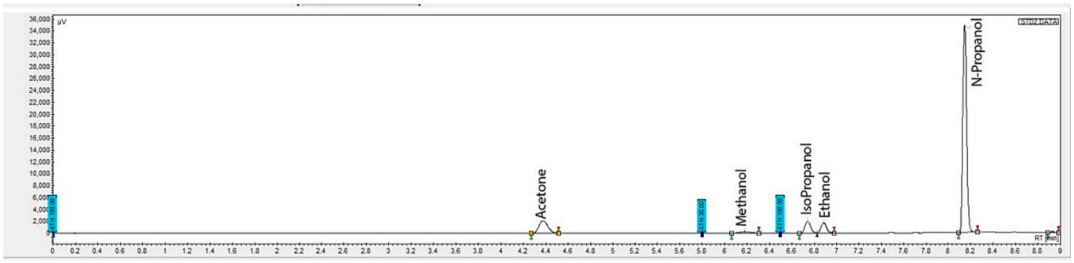

Fig. 2. Chromatogram for the LOQ of GC-HS.

Table 3
Results of methanol analysis in blood, urine, and vitreous humor. NA, not available.

No, of cases	Type of cases	Results of blood samples mg/dL	Results of urine samples mg/dL	Results of VH samples mg/dL
1	1st ER Sample	NA	9.1	NA
2	2nd ER Sample	6.0	7.5	NA
3	3rd ER Sample	NA	20.9	NA
4	1st Post-mortem Sample	118	225	116.3
5	2nd Post-mortem Sample	257	276	283

Table 4
Results of ethanol analysis in blood, urine, and vitreous humor. NA, not available; ND, not detected.

No, of cases	Type of cases	Results of blood samples mg/dL	Results of urine samples mg/dL	Results of VH samples mg/dL
1	1st ER Sample	NA	ND	NA
2	2nd ER Sample	NA	ND	NA
3	3rd ER Sample	NA	22.7	NA
4	1st Post-mortem Sample	0.598	0.178	0.231
5	2nd Post-mortem Sample	8.219	0.255	0.52

6. Institutional review board statement

The present study was approved by the Institutional Review Board (IRB) committee of Naif Arab University for Security Sciences, Riyadh, Saudi Arabia (NAUSS-REC-23-10). The proposed work was conducted following the procedures of the IRB Committee. The participants or their relatives signed the consent forms and agreed with the study investigations. Our work was performed in accordance with the guidelines of the rules of the Declaration of Helsinki of 1975 and later amendments.

Funding

This work was supported by the researchers supporting project number (RSP2024R235), King Saud University, Riyadh, Saudi Arabia.

CRediT authorship contribution statement

Sattam A. Alnefaie: Data curation, Writing – original draft, Writing – review & editing, Visualization, Investigation, Validation, Formal analysis, Methodology, Project administration, Software. **Abdulaziz A. Aldlgan:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Investigation, Supervision, Resources, Project administration, Software. **Khalid M. Albakiri:** Data curation, Validation, Formal analysis, Methodology, Resources, Project administration, Software. **Mohammed A. Kaabi:** Data curation, Validation, Formal analysis, Methodology. **Ghada M. Alzwen:** Data curation, Validation,

Formal analysis, Methodology. **Sarah S. Al-Otaibi:** Data curation, Validation, Formal analysis, Methodology. **Fawaz Alasmari:** Funding acquisition, Writing – original draft, Writing – review & editing, Resources, Project administration, Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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