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CASE SERIES

Methanol related death in National Institute of Forensic Medicine, Hospital Kuala Lumpur: A case series

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Abstract

Introduction: Methanol is a widely available chemical with a range of uses including as solvent, as a fuel, in chemical synthesis and anti-freeze preparations. Most of the cases are accidental exposures to drinking beverages contaminated with methanol. *Materials and Methods:* In mid-September 2018, there was a single outbreak of methanol poisoning in Malaysia especially involving the state of Federal Territory Kuala Lumpur and Selangor. There were 33 reported deaths suspected due to methanol poisoning in this current outbreak where 11 of them were brought in to the Institute of Forensic Medicine (NIFM), Kuala Lumpur. The last outbreak was in the year 2013 with 29 deaths reported out of 44 cases. *Results:* There were 3 cases (27.2%) died in hospital and the remaining 8 cases (72.8%) were found dead at home and were later brought in dead to the hospital. A full autopsy was carried out for each case. Autopsy findings, as well as lab results pertaining to cases that survived and directly brought in dead, were of a different spectrum. *Conclusion:* Methanol related deaths are almost always as a result of greed. The running truism is 'methanol poisoning is a result of deliberate addition/adulteration with industrial methanol'. Prevention of the illegal production of methanol and methylated spirits should be established to curb this matter in the future.

Keywords: methanol poisoning; putamen red infarct; putamen necrosis; lethal dose of methanol

INTRODUCTION

Methanol is also known as methyl alcohol (CH_3OH) or wood alcohol is adulterated in a cheap and potent illicit liquor such as Columbian spirit, Manhattan spirit, pyroxylic spirit, "derail" and "sterno". Methanol is a widely available chemical with a range of uses including as solvent, as a fuel, in chemical synthesis and anti-freeze preparations.[1] Acute or chronic poisoning may be produced by ingestion, cutaneous absorption or inhalation. In mid-September 2018, there was a single outbreak of methanol poisoning in Malaysia especially involving the state of Federal Territory Kuala Lumpur and Selangor. There were 33 reported deaths suspected due to methanol poisoning in this current outbreak where 11 of them were brought in to the National Institute of Forensic Medicine (NIFM), Kuala Lumpur.[2] The last outbreak was in the year 2013 with 29 deaths reported out of 44 cases.[3]

Methanol is a potent neurotoxic substance that causes severe metabolic acidosis and serious neurological disorders. Most of the cases are accidental exposures to drinking beverages contaminated with methanol. There are few articles reporting pure methanol intoxication; however, it is well known that small quantities of pure methanol cause blindness and death, the minimum lethal dose being 50–100 ml.[4] The nervous system has increased susceptibility for methanol intoxication. Methanol, through its chief metabolite, formate, causes irreversible neurological damage. Methanol intoxication produces classic neuropathological changes and characteristic imaging findings.

From the previous study in India during 1988, CNS involvement and renal changes were the most consistent findings and were seen to a variable extent in the 28 fatal cases due to methanol poisoning. CNS symptoms were predominant (75% of cases) and shock either at admission or as a late event was seen in 89% of

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the cases. Blurring of vision was seen in 42.8% and blindness in 10.7% of cases. Shrinkage and degeneration of parietal cortical neurons were the commonest findings (85.7%) whereas temporal cortex (28.5%), cerebellar granular layer (32.1%) and Purkinje cells (28.5%) were affected less often. Putamen degeneration and necrosis were also reported. Changes in the optic nerve and retina showed a paucity of documented autopsy data. Variable affection of other organs observed such as pulmonary oedema, cloudy changes in the myocardium, congestion and patchy haemorrhage in the stomach mucosa, acute pancreatitis and fatty changes in the liver.[5]

From another total of 17 cases in Turkey during the last decades, 8 cases (47%) presented with cerebral oedema and 9 cases (53%) presented with occipital, temporal and parietal cortex, basal ganglia and pons, petechial bleeding. In addition to these findings, haemorrhagic necrosis was observed in thalamus, putamen, and globus pallidus in 5 cases (29.4%) and, in the cerebral cortex in another 3 cases (17.6%). From those cases with cerebral oedema was found, herniation findings accompanied to the situation and pons bleeding (11.7%) was also observed. Around the basal ganglia with haemorrhagic necrosis, the situation could be ended with a ventricular compression (11.7%). There were 41% of the cases presented with chronic ischaemic changes association in cortical neurons, lacunae formation, degeneration of granular cell layer of the cerebellum, and reactive gliosis was considered as the results of chronic alcoholism.[6]

The aim of this study is to investigate various pathological changes of methanol intoxication so as to enable early diagnosis on the signs and symptoms of methanol poisoning, create awareness about the dangers of methanol poisoning as well as to alert the authority in regards to the illegal production of methanol and methylated spirits. As for the forensic department, taking a good history will raise the suspicion of methanol related death which further confirmed by sending necessary investigations after performing a thorough autopsy.

MATERIALS AND METHODS

There were 11 fatal cases with the suspicion of methanol poisoning brought to the National Institute of Forensic Medicine (NIFM), Kuala Lumpur. A full postmortem examination was performed for each case following the standard and guideline. Blood, urine, vitreous humour and gastric content sent to Chemistry Department Malaysia for further laboratory testing. The laboratory investigation involved qualitative and quantitative analysis using the analytical method namely solid-phase microextraction (SPME) and static headspace sampling coupled with gas chromatography and flame ionization detector (GC-FID) due to its volatility of methanol. The quality control and method validation of the analytical test is widely accepted and adhered to the standard at par with ASCLD accreditation. Relevant histology from every organ was studied under the microscope to detect any pathological changes arising as a consequence of methanol poisoning or to determine if the disease arising independently so as to associate with the findings of the gross examination.

Ethical Consideration

We have registered the case series with National Medical Research Registry [NMRR-19-1929-46175] after their review and we also have obtained publication approval [KKM. NIHSEC.800-4/4/1 Jld. 71(38)] from the National Institute of Health (NIH). All the postmortem examination were performed with the Police Order 61 issued and the laboratory investigation was part of the standard operating procedures. This was the retrospective case series report that not involved any clinical intervention whereby the autopsy findings and laboratory findings were revealed without any identifiable contents. It was considered less than minimal risk and absence of any ethical issues.

RESULTS

Clinical symptoms

Central nervous system (CNS) involvement in the form of unconsciousness, semi-consciousness, dizziness and visual symptoms were the predominant presenting features. Minimum fatal period was around half a day but the majority death occurred within 48 hours from the time of consumption of the adulterated alcohol. The symptomatology noted in most of our cases was very similar to the reported series.

Autopsy findings

There were 33 reported deaths suspected due to methanol poisoning in this current outbreak where 11 of them were brought in to National Institute of Forensic Medicine (NIFM), Kuala Lumpur as listed in Table 1. The total fatalities were male with the age range from the twenties

TABLE 1: Clinical presentation of cases with methanol poisoning

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Age	34	31	40	41	27	35	20s	42	38	42	50
Nationality	Foreigner	Foreigner	Local	Foreigner	Foreigner	Foreigner	Foreigner	Local	Foreigner	Foreigner	Local
Gender	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Co-morbidities	NIL	Unknown	Alcoholic	NIL	NIL	NIL	Unknown	NIL	Unknown	Unknown	Smoker and alcoholic
Period of survival	NIL	NIL	Unknown	NIL	NIL	NIL	10 hrs	NIL	3 days plus in ward	NIL	3 days in ward
Chief complaint	Blurring of vision and lethargy	Un-responsive	Found dead at home	BID	NIL	Drinking night before	Vomiting, abdominal pain, blurring of vision	Vomiting for 1 day	Cramping of limbs and fitted	Un-responsive	Vomiting and feverish 1 day
Range of timing from last drink (period of ingestion)	2-3 days	Unknown	Unknown	12-24 hrs	12-24 hrs	12-24 hrs	1 day from admission	Unsure (< 24 hrs)	1 day from admission	Unknown	1 day from admission

to fifties. Three of them were locals while the remaining were foreigners originated from Myanmar, Bangladesh and India. Regarding the distribution of the places of death, there were 3 cases (27.2%) died in hospital and the remaining 8 cases (72.8%) were found dead at home and were brought in dead to the hospital. The period of survival (treated in hospital) were ranging from 10 hours to 3 days. The investigations throughout the hospital stay portrayed features of metabolic acidosis.

Autopsy examination was performed on all of the cases. The deceased were all with average build (normal BMI). The previous medical illness was insignificant. Externally, no injuries were seen over the bodies. The cases that were brought in dead showed oedema of the brain with obliteration of the sulci and effacement of the gyri (Fig. 1A). The lungs were much congested and oedematous with each side weighing 550-800 grams (Fig. 1B). The liver showed patchy fatty changes in a few cases. (Fig. 1C). Otherwise, all the other organs were congested. Bilateral red infarction of the putamen (Fig. 1D) was noticed in one of the cases which managed to survive almost a day old under the intensive care unit (ICU). On top of that, bilateral putamen necroses (Fig. 1E) were observed in two of the cases which managed to survive up to 3 days in the intensive care unit.

Laboratory Findings

The results from laboratory investigation on the biological samples including blood, urine, vitreous humour and gastric contents were shown in Table 2. The range of methanol levels for brought in dead cases were from 91–605 mg/100mL (Median: 163 mg/100mL), 103–779 mg/100mL (Median: 209 mg/100mL) and 182–412 mg/100mL (Median: 270 mg/100mL) for blood, urine and vitreous humour respectively. The ranges of methanol levels for dead in ward cases were from 0–63 mg/100mL, 0–21 mg/100mL and 0–81 mg/100mL for blood, urine and vitreous humour, respectively. Ethanol is sometimes denatured (adulterated), and made poisonous, by the addition of methanol. The result is known as methylated spirit, "meths" (British use) or "metho" (Australian slang). Some of the seized methylated spirits and illicit liquors from the scene of death as well as throughout the investigation were detected positive with methanol.

DISCUSSION

Methanol is oxidised to formaldehyde and then quickly further oxidised to formic acid. It is these metabolic products, which have a toxic action. The time interval between the ingestion of the adulterated drink and the presentation with symptomatology is influenced by various factors. The latent period between consumption

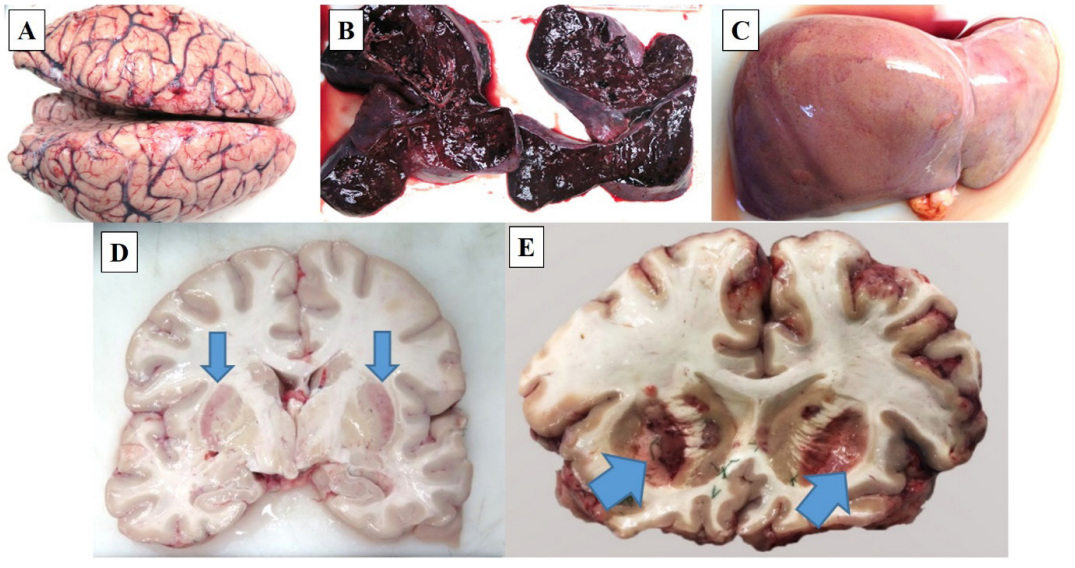

FIG. 1: The gross findings of methanol related death during postmortem on brain (A,D,E), lungs (B) and liver (C).

TABLE 2: Results from the laboratory investigation on the biological samples

Biological Samples	Blood mg/100 mL	Urine mg/100 mL	Vitreous Humour mg/100 mL	Gastric
Case 1	91	103	Not available	Not detected
Case 2	122	172	Not available	Not available
Case 3	605	779	Not available	Not available
Case 4	430	602	412	Not detected
Case 5	163	212	182	Not available
Case 6	328	466	389	Not detected
Case 7*	63	Not available	81	Not available
Case 8	320	206	358	Not available
Case 9*	Not detected	Not detected	Not detected	Not available
Case 10	417	521	452	Not available
Case 11*	11	21	14	Not available

*Samples were collected only during postmortem examination. Ante-mortem methanol analysis was unavailable.

of the drink and development of symptoms was variable (range 7.5–60 hours).[5] Methanol is rapidly absorbed from the gastrointestinal tract following oral administration with a mean absorption half-life of 5 minutes.[7] Depending upon the presence or absence of food, peak absorption occurs within 30–60 minutes.[8,9] After ingestion, methanol may persist in the body for as long as a week. It is water-miscible and distributes in total body water, therefore higher levels are attained in the aqueous and vitreous humour of the eye as compared to other body fluid. Co-ingested ethanol delayed methanol metabolism, hence resulted in longer latent period (12–72 hours).

The most probable mechanism of methanol-related deaths is sudden respiratory cessation due to histotoxic hypoxia caused by cytochrome oxidase complex inhibition. Symptomatology noted in most of our cases were very similar to the reported series.[5,6] Besides the direct toxic effects of metabolic products of methyl alcohol, the main effects are because of the metabolic acidosis, as is reflected in the decreased serum bicarbonate levels and pH of the blood. These were well documented in the 3 cases that survived for a period of time.

Putamen degeneration and necrosis were also reported in Mittal *et al*. (1991). Acute putaminal haemorrhage is a relatively rare complication and can be seen in methanol, carbon monoxide and ethylene glycol poisoning.[10] However, acute putaminal haemorrhage accompanied by visual loss and optic atrophy is known for its unique complications that appear only on methanol poisoning.[11] It is still unclear why haemorrhagic lesions especially well involve putamen in methanol poisoning. Most probably the accumulation of formic acid in the putamen is one of the causes.[12]

Methanol has a high toxicity in humans. As little as 10 mL of pure methanol when drunk is metabolized into formic acid, which can cause permanent blindness by destruction of the optic nerve whilst 15 mL is potentially fatal.[13] The median lethal dose is typically 100 mL (3.4 fl oz) equivalents to 1–2 mL/kg of body weight whilst minimal lethal dose is 0.3–1 g/kg of body weight.[14] The exact rates of morbidity and mortality from methanol intoxication are not available. The minimum fatal period was within 48 hours from the time of methanol consumption which is consistent with Mittal *et al*. (1991) where the minimum fatal period was 7 and 1/2 hours and the maximum was 12 days. This might due to the different source of illicit liquors with higher concentration of methanol were consumed. However, survival times ranged from several hours to days were consistent with Mittal *et al*. (1991). Methanol levels in blood and viscera were variable and similarly reported in previous studies. Mittal *et al*. (1991) reported that 14.3% of the cases presented with a significant amount of methanol in stomach contents 5–12 days after consumption of methanol, raising the question of re-secretion of methanol in the stomach. However, we encountered a limitation in the analysis of the stomach contents due to some technical issues and restricted resources.

The range of methanol levels for brought

in dead cases was consistent with the lethal dose portrayed in Table 3. However, the range of methanol levels for cases treated in wards i.e. Case 7 (Blood and Vitreous Humour) and Case 11 (Vitreous Humour) were exceeding the lethal dose. The main contributing factors that affecting the methanol levels would be the time of samples collection after the last consumption of methanol drinks as well as the treatment given in the ward management.

The blood methanol level was not detected in Case 9 which was a case treated about 3 days plus under the intensive care unit after consumption of suspicious drink one day before admission. Even if the time of ingestion is known, the blood methanol concentration does not correlate with the severity of the intoxication since the degree of acidosis is the major determinant of outcome. Once the diagnosis is established and treatment instigated, repeat serum methanol determinations are not helpful unless the intoxication does not resolve in the expected time. On the other hand, if the patients presented late, it may not be possible to demonstrate the presence of methanol. In the absence of methanol, diagnosis and treatment are based predominantly on history, acid-base status and exclusion of other metabolic causes.[15] Autopsy findings of a case which able to survive for a day and hence showed early changes (occurring 12–24 hours) after the insult in the form of red infarct of the bilateral putamen. Subacute changes occurring at 24 hours to 2 weeks include tissue haemorrhage and necrosis, which is seen in cases survived longer.

According to Zakharov *et al*, serum formate measurement can help in the laboratory diagnosis and clinical management of acute methanol poisoning. In their study of 38 patients from a Czech methanol mass poisoning in 2012, serum formate levels ≥3.7 mmol/L were seen to lead to the first clinical signs of visual toxicity, indicating haemodialysis. Serum formate ≥11–12 mmol/L was associated with visual/CNS sequelae and a lethal outcome. The probability of a poor outcome (death or survival with sequelae) was higher than 90% in patients with serum formate levels ≥17.5 mmol/L, serum lactate levels ≥7.0 mmol/L, and/or pH < 6.87.[17] This was also one of our limitation in this case series report as the metabolites were neither analysed for ante-mortem samples nor for post-mortem samples. Last but not least, the clinical history was solely based on the information gathered from various resources, hence subjected to incomplete data with relatively scarce information.

CONCLUSION

A good history taking will raise the suspicion of methanol related death which further confirmed by toxicological analysis. From the series of cases mentioned above, the brought in dead cases did not show any specific findings, which in reality these cases might be missed out if a toxicological analysis was not run specifically for methanol and its metabolites. On the other hand, those managed to survive under hospital care presented with changes in the brain. Methanol related deaths are almost always as a result of greed. The running truism is 'methanol poisoning is a result of deliberate addition/adulteration with industrial methanol'. Prevention of the illegal production of methanol and methylated spirits should be established. Methanol related deaths can be prevented by increasing the awareness in the whole country for example through public education in regards of harm of methanol as well as its products. Doctors, on the other hand, must be educated about methanol poisoning, in order for them to be aware of the symptoms as well as treatment of the patients.

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TABLE 3: Lethal dose of methanol poisoning[14]

Biological Samples	Methanol Lethal Dose
Blood	23–460 mg/100mL
Urine	30–612 mg/100mL*
Vitreous Humour	12–173 mg/100mL
Stomach Contents	73 mg

*Deduced from the alcohol excretion rate at the ratio of 1.33:1 (Urine:Blood)

Funding Resource: There is an absence of funding required for this case series reporting as postmortem examination and laboratory testing are part of the death investigation procedure.

Conflict of Interest: We wish to declare that we do not have any conflict of interest throughout this case series report and it is truthful findings for knowledge-sharing purposes.

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