A rare case of fatal materno-fetal methanol poisoning. Volatile congeners analysis as forensic evidence

Harald Jung*, Andreea Idor, Matei Dumitru Bucur, Adriana Jung, Arthur A. Keresztesi

Abstract: Background. Methanol intoxication may be the result of either accidental or intentional ingestion, in case of substantial exposures coma and death may occur. Methanol poisoning during human pregnancy was rarely described.

Material and method. We present the case of a 39-years old pregnant woman hospitalized for severe methanol intoxication. We reviewed the entire hospital medical documentation and performed blood and gastric content analysis for alcohol congeners using validated headspace-gaschromatography method (samples collected at admission from mother and at autopsy from fetus); we also examined all organs of the mother and of the stillborn, including microscopic sections stained with haematoxylin-eosin.

Results and discussions. The 34 weeks pregnant patient was transported to the hospital due to respiratory distress, lethargy and coma. Laboratory findings revealed metabolic acidosis with anion gap. At presentation intrauterine fetal death was diagnosed and the fetus was extracted next day. The woman died after four days in hospital. At post-mortem examination we found marked brain edema, brain stem hemorrhages, focal bleedings in the white matter of the temporal and parietal lobes, leptomeningeal hyperaemia, kidneys with tubular necrosis and hemorrhages in renal cortex. Autopsy of the fetus revealed only leptomeningeal hyperaemia, suggesting a rapid death. Blood ethanol concentration was 1.03 g/l in mother and 1.98 g/l in foetus while methanol concentration was 1.72 g/l and 1.99 g/l respectively. Relatively high amounts of amyl-alcohol (2-methyl 1-butanol) in both samples indicate consumption of fruit distillate, while toxic blood methanol concentration can be explained only by contaminated beverage consumption.

Conclusions. Intrauterine fetal death may occur without important morphological lesions in case of methanol transplacentar intoxication. Methanol is rapidly transferred to the fetus and cumulates in fetal circulation, while in case of other volatile congeners the transfer through the placental barrier seems to be selective.

Key Words: methanol, materno-fetal, pathology, volatile congeners.

Methanol is a clear, colorless and easy inflammable liquid, having rather a burning but not unpleasant taste. It has a molecular weight of 32.04 and its density is 0.781; the physical and chemical properties bring methanol closer to water than ethanol, making it soluble in water while its affinity towards fat tissue is low. The reparation in the body fluids is similar to ethanol, being characterized by an average Widmark factor of 0.7 [1].

Acute toxicity from methanol manifests as central nervous system depression, followed by a latent period of varying duration from 8-36 hours and rarely up to two days. Subsequently, metabolic acidosis develops, superimposed with headache, nausea and features of ocular toxicity. Coma and death may occur after substantial exposures. The minimum lethal dose following ingestion is considered to be in the range of 300-1000 mg/kg or a quantity of 50 – 100 ml of pure

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methanol [2, 3, 4, 5]. Several studies focusing on fatal methanol intoxication cases demonstrated an absolute prevalence of male gender, ranging between 80 – 90% [6, 7]. Women's exposure is rare, and intoxication during pregnancy is an exceptional occurrence.

Transplacental transfer and metabolism influence the extent of fetal toxicity, in case of methanol the main characteristics that facilitate transfer across the placenta are: low molecular weight, low protein binding and non-ionized state at physiologic pH [8]. The bi-directional fetal-maternal placental transmission is effective since the week 5 of intrauterine life. Any type of substance that reaches the mother's body, could reach the fetus's body too, in spite of the relative selectivity of placental barrier. Regarding potential toxicity of substances it is important if the transfer rate could build up to toxic levels in fetuses body. The evaluation of these "potentially toxic" levels is still unknown, as long as the fetal pharmacokinetics and the fetal pharmacodynamics are also unknown [9]. Maternal and/or fetal blood flow can be altered during gestation, in the context of umbilical cord anatomic variations (length, hypo- or hypercoiling), the thrombosis of subchorial vessels and the structure of perivillous fibrin deposition [10].

MATERIAL AND METHOD

In our case a forensic autopsy was performed for both the deceased mother and her stillborn, with macroscopic examination of all organs and histopathological examination of relevant fragment of organs formalin-fixed and paraffin-embedded, sections cut at five microns and stained with hematoxiline-eosine. All slides have been analyzed on a Leica DM 1000 optical microscope; digital images were acquired and processed with Leica Application Suite V4.0 program running under Windows XP Professional.

For the alcohol congener analysis (including methanol) we used a "Konik" gas-chromatograph with flame ionization detector, capilar Optimawax column (length 30 m), the carrier gas was nitrogen with a pressure of 10 ml/min, split injection with ratio 1:5; as combustion gas we used synthetic air with hydrogen. Detector temperature was 260° C and injector temperature 250° C. The resulted signals have been processed with a Hewlett Packard data acquisition system using DDS Clarity Master Software package. The method was previously validated in terms of specificity, linearity, accuracy, precision, limits of detection and quantification.

CASE REPORT

History

A 39 year-old woman, in her fourth pregnancy, at 35 weeks of gestation, is taken by the ambulance and hospitalized at 9.40 am at her local hospital at the Emergency Department with a 4 points Glasgow Coma Scale, a pulse rate of 80/min, with a blood pressure of 137/76 mmHg and a glycaemia of 127 mg/dl. Her husband denied alcohol consumption; she was lethargic and in respiratory distress.

The woman was intubated and mechanically ventilated, her blood pressure was observed, EKG, sample of blood, urine and stomach contents were collected for toxicological investigation.

At 9.40 am the emergency obstetrical consult and the ultrasonography of the abdomen and fetus revealed 35 weeks pregnancy, cranial fetal presentation, fetal death (fetal heart beats – absent, absence of fetal movement), without double skull contour, anterior placenta, normal amniotic fluid, normal uterine tonus, without painful uterine contractions, right Bartholin's cyst.

Results of laboratory tests included an arterial pH of 6.750, a partial pressure of carbon dioxide of 38.3 mmHg, a partial pressure of oxygen of 65.6 mmHg, an arterial oxygen saturation of 60.6 %, hyperpotassemia (potassium 6.12 mmol/l), hypocalcemia (calcium 0.87 mmol/l), sodium 144.7 mmol/l, chloride 108.9 mmol/l, and an anionic gap of 30.5 mmol/l.

The initial diagnosis was “Profound coma of unknown aetiology. Suspicion of unknown intoxication. Suspicion of pulmonary embolism. Sinus tachycardia. Severe metabolic acidosis. 35 week pregnancy stopped in evolution”. The CT angiography excluded pulmonary embolism. It was decided the transfer of the patient with the helicopter to the regional emergency hospital.

The patient was admitted at 2.44 pm at the regional emergency hospital where it was appreciated that the patient was not an obstetrical emergency. Initial management included hemo-hydro-electrolytic solutions, diuretics and anticoagulants. On day 2 of hospitalization, a hemodialysis session was practiced. A second ultrasonography, at 5 pm day 2, revealed cranial fetal presentation, fetus with biometry data corresponding 34 weeks of gestation, asystolia, without fluids in the pleural, pericardial or peritoneal cavities, without superimposition of parietal bones, without changes corresponding with an earlier death, normal amniotic fluid, anterior placenta, absence of the retroplacental haematoma.

The surgeon decided and practiced the treatment of the Bartholin's cyst, followed by a C-section for preventing the apparition of the intra-uterine fetal death syndrome. A 2400 g male was delivered, Apgar score was 0, absence of maceration signs. Because of uterine atony and massive hemorrhage from the hysterorhaphy cut, the C-section was followed by a subtotal hysterectomy without oophorectomy.

During hospitalization, the female had persistent metabolic acidosis, in the evening of day 4 she presented episodes of extreme bradycardia and asystolia without response to resuscitation manoeuvres and died. Detailed daily laboratory data are presented in Table 1.
Autopsy of the mother

The autopsy revealed brain edema, brain and brain stem hemorrhages, focal hemorrhages in the white matter of the temporal and parietal lobes, bilateral hydrothorax, a large number of petechia in the visceral pleura and visceral pericardium, lungs with fluid overload, liver dystrophy, bilateral diffuse renal cortical hemorrhages, anaemic organs.

The placenta was delivered to autopsy in formalin solution, the examination did not reveal any pathological changes.

Microscopic findings: sections of brain and brain stem revealed leptomeningeal hyperaemia (Fig. 1), marked edema, focal hemorrhages in the white matter of the temporal and parietal lobes, pontine hemorrhages (Fig. 2), fibrin microthrombus; the lungs showed denudation of respiratory epithelium, bronchiolitis, desquamative alveolitis, foci of bronchopneumonia – in different stages of evolution, edema, hyperaemia; hepatic anemia; microscopic examination of the kidneys revealed tubular necrosis (Fig. 3), hemorrhages and cortical hyperaemia (Fig. 4).

The toxicological findings (GC-HS method) from the blood samples collected at the time of hospital admission are represented in Table 2. The chromatogram for volatile congeners is shown in Fig. 5. Blood ethanol concentration was 1.03 g/l. Gastric content was also collected, analyzed and methanol together with volatile congeners has been identified.

<table>
<thead>
<tr>
<th>Hospital day</th>
<th>pH</th>
<th>Haemoglobin</th>
<th>K</th>
<th>Na</th>
<th>Ca</th>
<th>Chloride</th>
<th>Lactate</th>
<th>Bicarbonate</th>
<th>Anion gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.795</td>
<td>11.3</td>
<td>6.3</td>
<td>137</td>
<td>0.76</td>
<td>108</td>
<td>83</td>
<td>5.3</td>
<td>23.7</td>
</tr>
<tr>
<td>2</td>
<td>7.155</td>
<td>7.5</td>
<td>3.1</td>
<td>154</td>
<td>0.97</td>
<td>116</td>
<td>27</td>
<td>16.7</td>
<td>21.3</td>
</tr>
<tr>
<td>3</td>
<td>7.335</td>
<td>9.9</td>
<td>3.8</td>
<td>151</td>
<td>1.02</td>
<td>116</td>
<td>18</td>
<td>20.0</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>7.200</td>
<td>8.7</td>
<td>5.2</td>
<td>169</td>
<td>NA</td>
<td>125</td>
<td>NA</td>
<td>22.2</td>
<td>21.8</td>
</tr>
</tbody>
</table>

Reference values

- pH: 7.350 – 7.450
- Haemoglobin: 11.5 – 16.0 g/dl
- K: 3.4 – 4.5 mmol/l
- Na: 136 – 146 mmol/l
- Ca: 1,15 – 1,29 mmol/l
- Chloride: 98 – 106 mmol/l
- Lactate: 5 – 14 mmol/l
- Bicarbonate: 22 – 28 mmol/l
- Anion gap: 3 – 11 mmol/l

Table 1. Laboratory data of the methanol-exposed pregnant woman during her hospitalization

Figure 1. Leptomeningeal hyperemia (HE stain, 100x).

Figure 2. Foci of brain stem hemorrhage (HE stain, 50x).

Figure 3. Tubule necrosis in the kidney (HE stain, 100x).

Figure 4. Bleeding in multiple areas - kidney cortex (HE stain, 100x).
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Autopsy of the fetus (stillborn)

Male fetus weighing 2400 grams, length 48 cm, head circumference 34 cm; chest circumference 27 cm, abdominal circumference 32 cm, the umbilical cord 28 cm with a ligature at 8 cm from the body, with no pathological changes. The examination of the fetus did not reveal any pathological modifications, except for leptomeningeal hyperaemia. Pulmonary docimasia was negative.

The toxicology results from the blood samples collected during the autopsy (analyzed using GC-HS method) are to be found in Table 2. Blood ethanol concentration was 1.98 g/l (1980 mg/l).

Table 2. Toxicological result from blood analysis

<table>
<thead>
<tr>
<th>Alcohol volatile congener</th>
<th>Amount in mother's blood (mg/l)</th>
<th>Amount in stillborn's blood (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>1720 mg/l</td>
<td>1990 mg/l</td>
</tr>
<tr>
<td>Acetone</td>
<td>11.37 mg/l</td>
<td>3.26 mg/l</td>
</tr>
<tr>
<td>2-butanol</td>
<td>0.55 mg/l</td>
<td>Negative</td>
</tr>
<tr>
<td>1-propanol</td>
<td>0.51 mg/l</td>
<td>Negative</td>
</tr>
<tr>
<td>Isobutanol</td>
<td>2.10 mg/l</td>
<td>0.55 mg/l</td>
</tr>
<tr>
<td>1-butanol</td>
<td>11.04 mg/l</td>
<td>5.21 mg/l</td>
</tr>
<tr>
<td>Amyl-alcohol</td>
<td>15.70 mg/l</td>
<td>6.42 mg/l</td>
</tr>
</tbody>
</table>

The poisoning with methanol may result after either accidental or intentional ingestion. Symptoms of acute methanol poisoning are weakness, nausea, vomiting, headache, epigastric pain, dyspnea and cyanosis, while inebriation is not a prominent symptom. Stupor, coma, convulsions, hypothermia preceded death in fatal intoxications. Acidosis is the primary toxic factor and CNS depression is a relatively minor one.

The minimum lethal level in methyl alcohol poisoning is 0.8 g/l. Isopropanol is a congener with potential toxic CNS depressant effects that may come from outside (ingestion) or may arise through conversion from acetone in diabetics with ketoacidosis or in starvation cases with high levels of acetone. In such cases, there will be a high level of acetone and a low level of isopropyl alcohol [12]. In our case, the level of acetone was relatively low and no isopropanol was found, sustaining the exogenous source. However, elevated acetone levels can be found in cases of natural death (in absence of blood ethanol) with putrefaction due to microbial action, up to a concentration of 14.7 mg/dl [13].

Toxicity of methanol is due to its metabolites: formic aldehyde is responsible for the degeneration of the retina and optic nerve, liver, heart and kidney cells, whereas formic acid is a source of severe metabolic acidosis [14, 15]. Formic acid is six times more toxic than methanol [12]. Metabolic acidosis and anion gap are suggestive laboratory findings, detected in most cases of methanol intoxication [7]. Methanol poisoning during human pregnancy was rarely described in literature [16, 17].

DISCUSSIONS

Chronic maternal alcohol ingestion in pregnancy may cause fetal alcohol syndrome (FAS) manifested by prenatal and postnatal growth deficiency, microcephaly, specific craniofacial dysmorphic features (small eyes, upturned nose, micrognathia) [9, 11]. Different mechanisms have been offered to explain the toxicity of the alcohol, they include: decreased transplacental flux, increased local prostaglandins, direct action on placenta and fetal structures [9].

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The liver level of a derivative of the folic acid is one factor that regulates the elimination rate of formate. 15% to 30% of pregnant women are deficient in folic acid and may be susceptible to the toxic effects of the methanol [15]. Although methanol is metabolized through the same pathways in humans and animals, differences in the rate of formation of metabolic intermediates result in the marked variations in methanol-induced toxicity among species [15]. Studies in laboratory on rats and mice indicated that the rate of methanol metabolism by fetal liver in vitro was less than 10% that of the metabolic rate in adult liver [18].

The first documented methanol concentration in a fatal case of a human newborn, resulting from maternal exposure, was reported by Belson and Morgan in 2004; the infant died due to massive intraventricular bleeding day four after emergent C-section delivery while mother died on day ten due to acute respiratory distress syndrome and renal failure [16]. On the other hand, a case of non-fatal materno-fetal exposure to methanol was reported earlier, in 1997, by Hantson et al.: a young woman (in her 38th week of pregnancy) ingested methanol and the initial serum concentration was 2.30 g/l, together with a mild metabolic acidosis; no fetal distress was detected, it was decided to give tocolytic therapy until the treatment of methanol poisoning could be achieved in the mother.

Therapy included ethanol infusion, bicarbonate administration and three courses of hemodialysis. Delivery occurred six days after methanol exposure and no further complications were noted either in the mother or in her newborn [17]. Experimental studies on mice and rats (by determining amniotic fluid concentrations of methanol after intravenous administration to pregnant animals) revealed that the net rate of methanol translocation from maternal blood to amniotic fluid decreased as methanol concentration increased, possibly due to a methanol-induced decrease in blood flow to the fetus [15].

In series of 17 forensic autopsies performed on cases of methanol intoxication with lethal outcome after survival time ranging from eight hours to ten days, following lesions of the central nervous system have been reported: cerebral edema (in 47% of the cases, among them two cases with secondary pontine bleeding), petechial bleeding at occipital, temporal and parietal cortex, basal ganglia and pons (majority of the cases - 53%), hemorrhagic necrosis in thalamus, putamen, globus pallidus (29.4%) and in cerebral cortex (17.6%) [6].

Our findings also revealed brain swelling with secondary pontine bleeding foci, subcortical hemorrhages in the temporal and parietal lobes (autopsy of the mother); in addition leptomeningeal hyperemia was noticed in both mother and stillborn. In a study focusing on liver pathology, including 44 cases of fatal methanol poisoning, it has been shown that the most remarkable features of liver damage by light microscopy were: micro-vesicular steatosis, macro-vesicular steatosis, focal hepatocyte necrosis, mild intra-hepatocyte bile stasis, feathery degeneration and hydropic degeneration; in cases with mean blood and vitreous humor methanol levels greater than 1.27 ± 0.389 g/l more than one hepatic pathologic features were detected [19]. In our case we did not find any hepatic change, except for anemia in mother's liver; it is possible that at least part of the liver pathology found in fatal methanol intoxication cases might be explained by a history of alcohol consumption before the event.

Ingestion of pure methanol determines severe injuries to the upper digestive tract. Complete detachment of the oesophagus mucosa and brownish discolouration of the gastric mucosa with diffuse haemorrhagic necrosis of the stomach mucosa and intense acute inflammatory infiltration of the lamina propria have been described in a woman after suicidal ingestion of 500 ml absolute methanol that died 23 hours later due to metabolic acidosis and multiple organ dysfunction syndrome [4].

Death may be in some cases a direct result of acute necrotizing pancreatitis after methanol poisoning. Incidence of pancreatic damage has been reported up to 50% in methanol intoxication cases: acute methanol poisoning appears to produce pancreatic injury, although antidotal treatment with ethanol or prior chronic ethanol abuse may be contributing factors. Because ethanol treatment may complicate the pancreatic injury, fomepizole (4-methylpyrazole) may be the preferable antidote in acute methanol poisoning [20].

Methanol distribution in tissues and organs is variable, highest postmortem concentrations have been reported in brain and kidneys compared to venous femoral blood [21, 22], explaining the morphological changes on these sites, like we observed as well. However, fatal methanol intoxication resulting in a massive cerebral edema combined with a subarachnoid hemorrhage might determine brain death without renal injury, the person being eligible for organ donation (kidneys) based on imaging tests and biochemistry (renal morphology, circulation, creatinine levels, creatinine clearance) [5].

An even better indicator for severe methanol intoxication as an autopsy diagnosis is the concentration of formic acid, the main metabolite responsible for toxic effects. The technique recommended is GC-HS with FID detector, after previous transformation of formic acid in methyl formate. Formic acid concentration reached a maximum of 1.10g/l in a series of short-survival severe methanol intoxication cases and a good correlation between blood and brain, but poor between blood and the remaining tissues was found [23].

Volatile congeners analysis might be a good indicator for the type of alcoholic beverage ingested. Extremely high blood levels of methanol, n-propanol
in combination with amylalcohols (2 and 3-methyl-1-butanol) strongly suggest an intake of fruit distillates [24]. In our case, the relatively high level of amylalcohol (15.70 mg/l) hints for a fruit distillate, considering also our previous study which did not reveal high propanol concentrations in Romanian home-made or marketed brandies [25]. In the same time, the toxic level of methanol indicates likely consumption of a contaminated beverage. In such situations, it is advisable to analyse remains of the consumed beverage as well; this investigation was not requested by the Police in our case.

CONCLUSIONS

In case of methanol intoxication multi-organ involvement is possible, primarily affected being the central nervous system. Severe matero-fetal methanol intoxication may result in intrauterine fetal death without significant morphological lesions. Methanol is rapidly transferred to the fetus and cumulates in fetal circulation, while in case of other volatile congeners the transfer through the placental barrier seems to be selective.

Volatile congeners analysis may give an indication on the type of alcoholic beverage consumed, in our case amyl alcohol was suggestive for fruit distillate.

References