Study Regarding Correlation of the Methanol Intoxication and Tissues Necrosis

ANTON KNIELING[1,2], MIOARA CALIPSOANA MATEI[1]*, DIANA BULGARU ILIESCU[1,2], CRISTIANA MANEA[3], MADALINA DIAC[1,2], RALUCA OZANA CHISTOL[1,4]*, CRISTINA FURNICA[1,2]

[1] Grigore T. Popa University of Medicine and Pharmacy, 16 Universitatii Str., 700115, Iasi, Romania

[2] Institute of Forensic Medicine, 4 Bunavestire Str., 700455, Iasi, Romania

[3] Alexandru Ioan Cuza University of Iasi, Faculty of Geography and Geology, 22 Carol I Blvd., 700506, Iasi, Romania

[4] Cardiovascular Diseases Institute, 50 Carol I Blvd., 700503, Iasi, Romania

Methanol intoxication is a potentially fatal medical condition associated with basal ganglia and subcortical white matter necrosis. The authors present the case of a 34 years-old female with putaminal necrosis and haemorrhagic stroke secondary to methanol intoxication. The patient was hospitalized in the intensive care unit with severe metabolic acidosis and bilateral blindness after ingesting an unspecified amount of methanol. Computed tomography (CT) examination performed at hospital admission revealed a hypodense, inhomogeneous aspect of lenticular nuclei with ischemia in observation. In the 18th day post-ingestion the patient went into deep coma and a new CT examination was performed revealing an intracerebral hematoma involving the right lenticular nucleus, right external and extreme capsule, and right insula with uncal herniation. Neurosurgical decompression was attempted with unfavourable outcome and exitus. Necropsy examination revealed bilateral lenticular necrosis and a hematoma between the base of the right lenticular nucleus and insular cortex with destruction of the claustrum, external and extreme capsules. Methanol poisoning (mostly accidental) is not uncommon in our country and its metabolite, the formic acid, is a potent central nervous system toxin. Bilateral lenticular necrosis is a typical finding in methanol intoxication due to formic acid accumulation with decrease in mitochondrial adenosine triphosphate (ATP) synthesis responsible for cellular toxicity.

Keywords: methanol, formic acid, intoxication, lenticular nuclei, necrosis

Methanol (CH_3OH), methyl alcohol or wood alcohol, is a low molecular weight alcohol with multiple applications both in industry and household environment, toxic, clear and flammable liquid at room temperature, not suitable for human consumption. Methanol is a domestic product included in the composition of antifreeze solutions, solvents, fuels and alcoholic disinfectants. Poisoning is accidental in most cases (ingestion secondary to confusion with ethanol, counterfeit alcoholic drinks) or due to a suicide attempt [1, 2].

Methanol intoxication is very severe with deep coma, irreversible sequelae (scotoma, blindness, Parkinson like syndrome, polyneuropathies) and potentially fatal (22-36% of cases) occurring almost exclusively after oral intake, although the transdermal and pulmonary absorption may also lead to severe symptoms [1]. The number of carbon atoms, the molecular weight and the boiling point place methanol at the bottom of the increasing toxicity scale of alcohols. Despite its accessibility, intoxication with this product is rare today (its real incidence is unknown), sporadic cases being described with very high mortality. Early diagnosis is crucial to adequate treatment and often difficult as initial symptoms are similar to ethanol consumption.

The authors report a particular case of bilateral lenticular toxicity and unilateral haemorrhagic stroke following methanol ingestion with a poor outcome (death).

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* *email: mat_calipso@yahoo.com; ralucachistol@gmail.com*

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Experimental part

A 34-year-old female with no particular personal history was hospitalized in the Intensive Care Unit (ICU) following transfer from a county hospital 5 days after ingestion of an unspecified quantity of methanol. The admission diagnosis was severe metabolic acidosis, methanol intoxication, optic neuropathy and bilateral blindness.

Computed tomography (CT) examination performed upon admission revealed a hypodense, inhomogeneous aspect of lenticular nuclei with ischemia in observation. Ophthalmic examination indicated a prominent, white and oedematous optic nerve papilla and the absence of the pupillary light reflex thus sustaining the diagnosis of optic nerve atrophy secondary to methanol intoxication.

The patient was confused, agitated, with a blood pressure of 90/60 mm Hg and needed intubation, mechanical ventilation and vasopressor support. Initial lab results were suggestive for severe metabolic acidosis (alkaline reserve 11%, *p*H = 7.28, H_2CO_3 14 mmol/L, lactic acid 1.2 mmol/L) and dyselectrolytemia (hyponatremia and hypopotassaemia). The patient registered a relatively stable evolution with dyselectrolytemia and acidosis correction but no neurological improvement.

A second CT examination was performed 11 days post-ingestion and displayed an extension of previously described lesions to right insula, corona radiata, right thalamus, right cerebral peduncles, mesencephalon, pons and right cerebellar hemisphere with diffuse cerebral oedema. In the 18th post-ingestion day the patient went into deep coma (Glasgow coma score 3) with anisocoria, abolished reflexes, arterial blood pressure 100/60 mmHg. A new CT examination performed the same day revealed a hyperdense area suggestive for haemorrhagic stroke affecting the right insula, external and extreme capsule and obscuration of the lenticular nucleus with associated oedema, mass effect, midline shift (uncal herniation), and compression of the frontal horn of the right lateral ventricle. Cerebral and cerebellar gyri were diffusely obscured. The hypodense aspect of basal ganglia, pons and mesencephalon was stable. Neurosurgical decompression was attempted (craniotomy) with poor outcome and exitus.

Necropsy examination revealed necrosis of lenticular nuclei (especially putamen) and a hematoma between the base of the right lenticular nucleus and right insula with destruction of claustrum, external and extreme capsules (fig. 1).

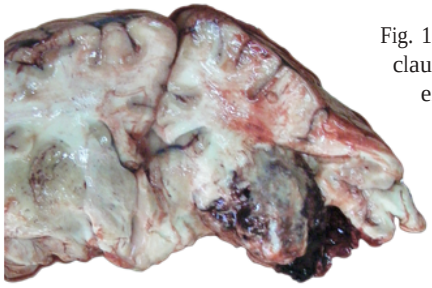


Fig. 1. Destruction of right claustrum, external and extreme capsules

Histopathological examination identified intra-parenchymal brain haemorrhage with conjunctive organisation, focal neuronal ischemia, oedema, and meningo-cerebral congestion. In the pons there were observed intraparenchymal perivascular haemorrhages, oedema and passive congestion (fig. 2).

Passive congestion and oedema was also revealed in case of optic nerve fibres (fig. 3).

Overall, histopathological examination was concordant with necropsy findings.

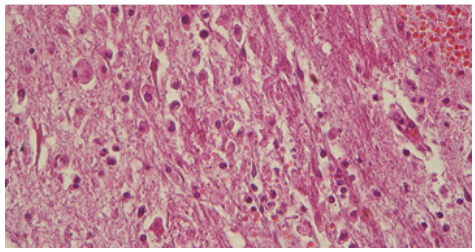


Fig. 2. Ischemic neuronal changes (HE, 400X)

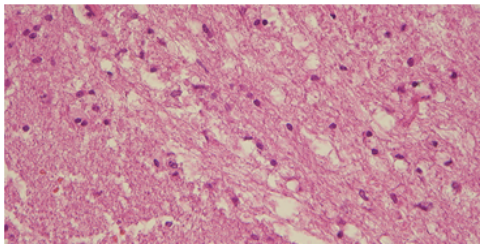


Fig. 3. Optic nerve fibres oedema (HE, 400X)

Results and dscussions

Generally, there is a latent period of 12–24 h between methanol ingestion and the onset of symptoms. It may be delayed further, up to 24-48 h depending on the quantity, concentration and concomitant ethanol ingestion [7].

After ingestion, methanol is readily absorbed from the gastrointestinal (15 min) and respiratory tracts with peak concentrations at 30-90 min and rapid diffusion in all tissues proportional to the water content. 90-95% of ingested methanol is metabolized in the liver and only 5-10% is being excreted unchanged by the lungs and kidneys. Lethal dose varies according to individual sensitivity between 30-100 mL of pure methanol ingested in a single dose. Generally accepted lethal dose is of 75 mL for a 75 kg adult while ingestion of only 15 mL can lead to blindness. Excretion rate also varies upon lung ventilation. By having low metabolising and excretion rates, methanol accumulates in the body thus increasing the toxicity of small, repeated doses [8].

For quantitative methanol determination in the blood, 2 mL of blood are mixed with 2 mL of trichloroacetic acid solution 20% followed by centrifugation at 2000 rotations/minute. 1 mL of the supernatant is collected in a test tube and 0.2 mL of permanganate solution (1.5 g permanganate + 50 mL water + 7.5 mL of 85% phosphoric acid) is added. After shaking the test tube for one minute, Na bisulfite is used to remove the excess of permanganate. Some crystals of chromotropic acid and 1.5 mL of sulfuric acid

are added to the solution. At the contact zone between the fluids a violet ring is formed. A gentle shaking diffuses the coloration, its intensity being proportional to methanol concentration in the blood. The blood without methanol colours in light brown [7].

In order to quantify methanol concentration, a 1 cm cuvette is filled-up with the solution and after 20 min the absorption of light at a wavelength of 575 nm is compared to the one obtained in case of a cuvette filled with similar reactives except the methanol replaced by 0.5 mL of water [7].

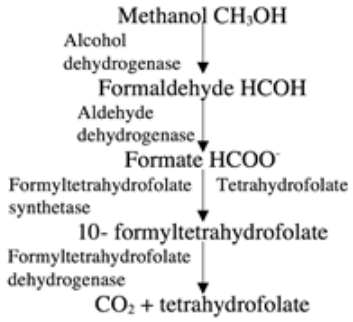
Methanol concentration is calculated using the following formula:

$$\text{Methanol (g‰)} = A_p \text{‰} \times 0.398$$

where A_p is absorbance of the probe, and 0.398 the slope factor

A methanol concentration >0.080g/L is considered dangerous.

Methanol toxicity is due to its metabolites: formaldehyde and formic acid (fig. 4). Formaldehyde is 150 times more toxic than methanol itself and may interact with protein amino groups (-NH_2) especially in case of enzymes. Formic acid triggers a severe metabolic acidosis (high affinity for ferruginous enzymes) and inhibits cellular respiration in sensitive tissues. Also, by inhibiting oxidative reactions, it promotes the anaerobic metabolism generating lactic and pyruvic acids which aggravate acidosis [9].



The clinical presentation of methanol intoxication is dominated by acidosis signs (Kussmaul dyspnoea, cardiorespiratory arrest), visual disturbances (blurred vision, fixed mydriasis, sudden or progressive blindness), cardiovascular symptoms (hypotension, bradycardia), neurologic symptoms (agitation, delirium, seizures, obnubilation, coma), gastrointestinal symptoms (nausea, vomiting, acute abdominal pain). In case of intoxication by ingestion, the coma is accompanied by tonic-clonic seizures and muscular hypertonia [10-12].

The symptomatology of methanol poisoning can initially be misleading since it mimics ethanol intoxication but with no alcoholic halitosis. The initial symptoms are represented by dizziness, weakness, somnolence, frontal and temporal headache. Six to 12 h later nausea, vomiting (sometimes hematemesis) and abdominal pain occur. Twelve to 24 h after the first signs, visual disturbances (decreased acuity, blurred vision and papillary oedema) and neurological signs evolving towards a deep coma and sometimes tonic-clonic seizures appear. Acidosis leads to tachypnoea or Kussmaul respiration as a compensatory mechanism. Acute methanol intoxication may progress to exitus due to nervous system depression (respiratory depression, cardiovascular collapse) [10, 13].

In case of severe intoxication, the onset can be acute with seizures, stupor, coma or exitus in the first hours after ingestion.

Neurological toxicity can be visualised at CT or magnetic resonance imaging (MRI) starting with 24 h after ingestion but there have been reported cases of delayed lesions onset or extension (variable number of days after ingestion). In the current literature, bilateral lenticular nuclei (especially putamen) necrosis/ischemia associated to optic nerve atrophy are considered typical for methanol intoxication [14-19].

Formic acid inhibits mitochondrial cytochrome oxidases and induces a decrease in mitochondrial adenosine triphosphate (ATP) synthesis responsible for cellular toxicity. The central nervous system is particularly sensitive to ATP decrease as it is required for the normal functioning of the various signal transducing systems including the Na+/K+ ATPases involved in electrical conduction. The decrease in Na+/K+ ATPase activity induces a diminishment of the axonal flow through the optic pathways with axonal stasis and papillary edema. In addition, axonal injury and swelling lead to compression lesions. Basal ganglia are particularly sensitive because of their intense activity requiring significant energy inputs [8] and the presence of striated neurons. Most frequently there are observed ischemic and haemorrhagic lesions of basal ganglia (especially the putamen) with oedema and demyelination of the neighbouring white substance [20, 21].

The association between lenticular ischemia/necrosis and white matter haemorrhagic lesions was first described in 1953 by Orthner and, in 1988, Phang et al. have objectified by CT imaging the haemorrhagic necrosis of basal ganglia and intraventricular haemorrhage in 6 of 21 patients with methanol intoxication [22, 23].

The exact aetiology of haemorrhagic transformation of lenticular ischemic lesions is not known and some authors attribute it to haemodialysis-associated heparinisation and haemodialysis-induced thrombocytopenia.

A study performed on various canine species at the State University of New York proved that methanol increases calcium ions concentration in the media of cerebral vessels thus inducing vasospasm. These events could trigger cerebral oedema, lenticular ischemia/necrosis and intraparenchymal haemorrhage in methanol intoxicated patients [24].

Systemic toxicity has also been described with haemolysis/rhabdomyolysis associated to secondary renal insufficiency, pancreatitis and acute hepatitis [9].

The aim of the methanol intoxication treatment is, on the one hand, the rapid correction of acidosis with alkaline solutions and, on the other hand, inhibiting the formation of formic acid and the elimination of methanol and its metabolites.

The first measure to be taken is gastric lavage which proves effective if performed early after ingestion. An eight-hour limit after ingestion seems reasonable, but given the large amounts of methanol found in the gastric fluid of untreated patients several days after the ingestion, some authors advocate longer delays [25].

The strategy to counter methanol toxicity is based on the fact that only its metabolite, formaldehyde, resulting from the action of alcohol dehydrogenase (ADH) that oxidizes methanol is toxic by itself and after conversion to formic acid (formate) via aldehyde dehydrogenase (ALDH). Ethanol has a 10-20 times higher affinity for ADH compared to methanol and is the preferred substrate. Diluted ethanol can be administered intravenously in order to bind to ADH and slow the metabolic chain methanol-formaldehyde-formic acid. Thus, methanol can be excreted unchanged by the lungs and kidneys or removed through hemodialysis. In order to be effective, ethanol administration should maintain a constant alcohol blood concentration of 1-1.5‰.

Hemodialysis using a bicarbonate dialysate also reduces acidosis and should be applied up to 10-15 h after negativity of blood samples for methanol [1, 7, 9]. To summarize, the treatment is mainly based on alkalinisation, reduction of ADH action by competitive inhibition, and methanol elimination.

Conclusions

Methanol poisoning (mostly accidental) is not uncommon in our country and its metabolite, formic acid, is a potent central nervous system toxin responsible for severe lesions with unfavourable outcome despite optimal treatment.

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