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CASE REPORT

Survival of a formalin intoxication: a case report

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Abstract

Formalin is an aqueous solution with formaldehyde, a colourless, water-soluble gas. Usually formalin contains methanol as a stabilising agent. The solution is often used as a disinfecting agent. A 85-year-old woman was admitted to the emergency department with altered levels of consciousness after she accidentally drank formaldehyde cleaning detergent. She was treated with intravenous folinic acid in order to increase the elimination rate of formic acid. However, she rapidly developed signs of shock with multi-organ failure requiring symptomatic treatment, including intubation, supportive vasopressor treatment and renal replacement therapy, and recovered with time and intensive treatment. The literature suggests that intoxication with formalin is fatal. We present a case of an elderly lady surviving a severe illness caused by a moderate formalin intoxication.

Introduction

In the literature, most case reports regarding formalin intoxications [1-6] describe high-dose formalin intoxication with a fatal end. The purpose of this paper is to describe the clinical treatment of formalin intoxication. Although our patient ingested a small dose (±1 gram) of this toxic substance in comparison with the fatal cases described (>10 gram formaldehyde), it still caused severe illness with multiple organ failure.

Case report

An ill 85-year-old woman, previously diagnosed with insulin-dependent diabetes mellitus, hypertension and chronic obstructive pulmonary disease GOLD-1, was referred to our emergency department (ED) with altered levels of consciousness. At the ED, we saw a somewhat drowsy patient, with thirst and mild abdominal pain as her chief symptoms.

She was approached according to the ABCDE protocol. There were no signs of airway obstruction. Signs of cyanosis were absent; SpO2 was 95% on room air, the breathing frequency was 14/min. Pulmonary examination showed no abnormalities. Circulatory examination revealed cold extremities, a capillary refill time of 5 sec, a blood pressure of 105/67 mmHg and a heart rate of 93/min, regular. Her abdomen was soft and non-tender. The Glasgow Coma Scale was 12 (E3 M6 V3), pupils were equal, round and reactive to light. There were no signs of lateralisation. Her body temperature was 35.4oC.

Laboratory investigation revealed a severe metabolic acidosis with elevated serum lactate levels and a widened anion gap *(table 1)*. The elevated serum lactate levels could not completely explain the widened anion gap. Because of the absence of ketonuria, we ruled out keto-acidosis. We considered she might have ingested a toxic substance.

Since our patient did not remember what had happened, we contacted her husband. He had found her an hour before she arrived at the ED, sitting at the table with altered levels of consciousness. Next to her he saw a soft drink bottle with an extra label with 'formaldehyde detergent', which he received years ago as a cleaning agent. She drank about 20 ml of the fluid in the bottle with a straw, and stopped drinking when she noticed a different taste.

Oral inspections showed no ulcerations but, as mentioned, our patient drank the fluid with a straw. She did not display the characteristic smell of formaldehyde. A serum ethanol was negative (<0.1 mg/l), but blood tests for toxic alcohols were positive for methanol, with a concentration of 70 mg/l. This was below the antidote treatment range of serum methanol (>200 mg/l).[13] Because of the usual combination of formalin and methanol in cleaning agents, the presence of methanol in

Table 1. Laboratory results of the patient

	t0	t1	t2	t3	
Haemoglobin (mmol/l)	11.4	11.4		5.4	mmol/l
Haematocrit (l/l)	0.56	0.53		0.26	l/l
Erythrocytes (10^12/l)	5.81				10^12/l
MCV (fl)	96				fl
RDW (%)	12.7				%
Thrombocytes (10^9/l)	280	221		640	10^9/l
Leucocytes (10^9/l)	30.9	20.9		18.7	10^9/l
Na+ (mmol/l)	139	145		146	mmol/l
K+ (mmol/l)	4.7	4.4		3.6	mmol/l
Cl- (mmol/l)	100	106		109	mmol/l
Urea (serum)	11.5	13.3		11.2	mmol/l
Creatinine (serum)	145	190		78	µmol/l
Albumin (g/l)	33	21		24	g/l
Osmolality (mOsm/Kg)		321			mOsm/Kg
pH	7.19	7.41	7.11	7.44	
pCO2 (kPa, mmHg)	4.0 (30)	4.0 (30)	7.6 (57)	4.9 (36.75)	kPa (mmHg)
pO2 (kPa, mmHg)	10.8 (81)	14.7 (110.25)	12.2 (91.5)	10.9 (81.75)	kPa (mmHg)
HCO3- (mmol/l)	11	19	18	25	mmol/l
Base excess (mmol/l)	-15.6	-4.5	-11	0.9	mmol/l
Lactate (mmol/l)	3.5	3.6	4.9	0.8	mmol/l
FiO2 (%)	21	22	100	30	%
Glucose (mmol/l)	14.6	14.7		7.2	mmol/l
Anion gap[1]	34.45	29.15		19.6	
Osmol gap[2]		3			

t0 = presentation at ED, t1 = admission at ICU, t2 = prior to intubation and start of CVVH, t3 = day of discharge to medical ward (no renal replacement therapy).
1. Anion gap calculated as ([Na+] + [K+] – ([HCO3-) + [Cl-]) + (0.25*(40-[Alb])).
In physical values:
t0: (139 + 4.7) – (11 + 100) + (0.25*(40-33))
t1: (145 + 4.4) – (19 + 106) + (0.25*(40-21))
t3: (146 + 3.6) – (25 + 109) + (0.25*(40-24))
2. Osmol gap calculated as serum osmolality - ((2 x [Na+]) + [glucose] + [urea]). In physical values: 321 – ((2 x 145) + 14.7 + 13.3)

her serum supported our presumed diagnosis of a formalin intoxication. The bottle was sent to the pharmaceutical laboratory for further analysis.

Due to the severe metabolic and lactic acidosis, an abdominal CT was ordered to exclude mesenteric ischaemia and perforation. This CT scan revealed an oedematous gastric wall with no signs of perforation. There were no signs of mesenteric ischaemia. The Toxicological Centre of the Netherlands (NVIC) and hospital pharmacology department were consulted for supplementary treatment advice.

For further evaluation and observation, our patient was initially hospitalised on the medical ward with 'accidental formalin auto-intoxication' as the most likely diagnosis. Treatment with intravenous folinic acid (1 mg/kg every 4 hours) was started to improve conversion of formic acid into carbon dioxide and water. In order to reduce the severe metabolic acidosis, sodium bicarbonate was added to the treatment.

The next day, she showed signs of shock with worsening hypotension and anuria. Our patient was admitted to the intensive care unit (ICU) for further treatment. In the first two hours after ICU admission, the metabolic acidosis was combatted with sodium bicarbonate. A gastroscopy was performed, revealing mild oesophageal and duodenal lesions and moderately severe gastric lesions. However, during this procedure aspiration occurred and respiratory failure because of worsening metabolic acidosis. Our patient was then intubated and sedated. A bronchoscopy to evacuate the aspirate fluids revealed no pathological tracheal or bronchial lesions. Laboratory investigation at that time showed severe metabolic acidosis and worsening of renal failure *(table 1)*, both interpreted in the context of formic acid and shock.

Laboratory analysis of the fluid in the bottle showed a watery fluid with 5.4% (54 mg/ml) formaldehyde and 4.9% (49 mg/ml) of methanol. She had swallowed approximately 20 ml; this means she ingested approximately 1080 mg of formaldehyde and 980 mg of methanol. Commercially available disinfecting agents with formaldehyde normally contain 37-50% formaldehyde and 8-15% methanol. The fluid our patient ingested contained lower concentrations, probably because of an evaporating process and water added.

We decided to start continuous venovenous haemofiltration (CVVH) to combat the severe metabolic acidosis and renal failure and to improve elimination of methanol and formic acid. The sodium bicarbonate was stopped the same day after the acidosis had improved during CVVH. Antibiotics (piperacillin/tazobactam 4 g/0.5 g 3 dd iv) were started because of aspiration and gastrointestinal lesions with signs of septic shock. Over the next few days, the patient showed both haemodynamic and respiratory stabilisation. Because of the improvement in anion gap and acidosis, the folinic acid could be stopped on the third day after ICU admission.

A second gastroscopy performed at the fourth day of the ICU stay showed gastric necrosis but no pathology in the oesophagus or duodenum. A nasal duodenal tube was inserted in order to start post-pyloric feeding. In the following days her condition improved. On day 5 of her ICU stay she was extubated. During the next few days her renal function improved with spontaneous diuresis and improvement of creatinine clearance *(table 1)*.

After 13 days, our patient was discharged to the medical ward for further recovery. A new gastroscopy was performed, which showed improvement of the gastric necrosis, with in fundo a superficial area with ulceration and centrally a partially black mucosa. The nasal duodenal tube was removed and our patient was allowed to expand her diet to normal. After a 29-day stay

in hospital, our patient was referred to a revalidation clinic for further recovery.

Discussion

Formaldehyde toxicology and kinetics

Formaldehyde is a colourless, water-soluble, pungent gas. Since the pure gas tends to polymerise, formaldehyde is stored in solution. An aqueous solution with formaldehyde is called formalin. As methanol is frequently used as a stabiliser in formaldehyde, one should be aware of methanol co-intoxication after ingestion of formaldehyde. The solution is often used as a disinfecting agent. Formaldehyde is also an endogenous, intermediary metabolite in mammals,[7] with an endogenous concentration <4 mg/l in human plasma.[8]

Formaldehyde has a high protein-binding capacity, probably caused by the high grade of chemical reactivity of formaldehyde with amino acid groups of proteins. Formaldehyde bonded to proteins is mainly metabolised to formic acid in the liver by hepatic aldehyde dehydrogenase *(figure 1)* and to a lesser extent

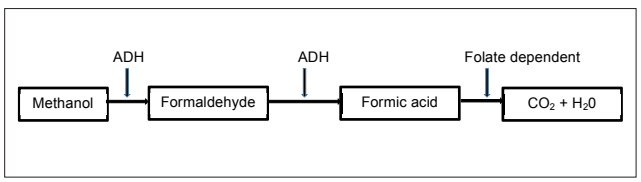

Figure 1. Metabolic pathway of methanol and formaldehyde

in erythrocytes, brain, kidneys and muscle. The conversion of formaldehyde into formic acid is rapid, resulting in an average plasma half-life of 90 seconds for formaldehyde.[7] The plasma half-life for circulating formic acid is 90 minutes depending on the urine pH and folic acid stores.[7] For the metabolism of formic acid to carbon dioxide and water, folate is necessary and is the speed limiting step.[7,9,10]

Ingestion of solutions containing formaldehyde can cause a varied number of both local and systemic symptoms. Local corrosive effects after ingestion can cause erythema, erosions, ulcerations and perforations in the mouth, laryngopharynx, oesophagus, stomach and duodenum, which can result in symptoms such as nausea, vomiting, abdominal pain and respiratory distress.[1,2] Later on diarrhoea, hematemesis and melena can develop. Even after weeks to months, stenosis of mainly the oesophagus and pylorus can occur[1] due to corrosive effects on the mucosa.

Systemic effects that can occur are shock, unconsciousness, convulsions and acute respiratory failure.[1,7,8,11] Formic acid may cause rapid coagulation necrosis and protein precipitation of cells in the heart, brain, kidneys and liver and tissue fixation. In severe intoxications, renal failure and anuria due to renal tubular necrosis are frequent complications.[8] Formic acid may also cause an anion gap metabolic acidosis. Many of these symptoms were observed in our patient.

Methanol co-intoxication

After co-ingestion of methanol, maximum methanol plasma concentrations are reached within 30-60 minutes. Methanol is metabolised to formaldehyde by alcohol dehydrogenase,[12] mainly in the liver (90-95%), and partly in the kidneys, retina and optic nerve. The resulting formaldehyde is metabolised to formic acid as described above. Since part of the methanol is metabolised in the kidneys, retina and optic nerve, this can cause local accumulation of formic acid and results in local toxic effects as vision disturbances, temporary or even permanent blindness and acute kidney failure.[12]

Shortly after ingestion (within 0.5-4 hours), methanol causes symptoms such as sedation, ataxia and unrestrained behaviour. After 12-24 hours (up to 48 hours after co-ingestion with ethanol), due to the conversion of methanol to formic acid, systemic symptoms such as headache, vomiting, stomach pain and coma and convulsions may occur. Methanol also increases the osmol gap.

After ingestion of formaldehyde with methanol as stabiliser, next to formaldehyde, methanol contributes to the acid base imbalance, since the oxidation of methanol to formic acid results in accumulation of lactic acids. Accumulation of both formic acid and lactic acids causes metabolic acidosis, which can lead to the typical Kussmaul breathing pattern and an increase of the anion gap.[7,12]

Treatment of a formalin intoxication

Due to the short half-life of formaldehyde, determination of the formaldehyde plasma concentration is useless in case of suspected formaldehyde intoxication. The presence of an anion-gap acidosis can contribute to the diagnosis of formaldehyde intoxication.[12] If available in the hospital, the blood concentration of formic acid and methanol can be determined.

There are no specific antidotes for intoxications with formaldehyde and, therefore, symptomatic treatment is advised. Active coal to inhibit absorption is not recommended by the NVIC[11] because the literature is not consistent and it will impede inspection by endoscopy.

Sodium bicarbonate can be used for the correction of metabolic acidosis. Intravenous administration of folinic acid (1 mg/kg every 4 hours) should be considered in intoxications with formaldehyde,[8,12] since the availability of tetrahydrofolate is the speed-limiting step in the elimination of formic acid, as described in the toxicology section. Folinic acid increases the elimination rate of formic acid.

Haemodialysis may be considered to remove the formic acid and methanol because these substances are water soluble. Haemodialysis is also used for correction of acidosis, electrolyte disturbances and kidney failure. Because of the high protein bonding of formaldehyde, this substance is not substantially removed by haemodialysis. Hantson et al.[13] studied formate kinetics in methanol poisoning and found an endogenous

formate elimination half-life of 205±90 minutes and haemodialysis formate elimination half-life of 150±37 minutes. Continuous arteriovenous haemofiltration or CVVH may be considered if haemodialysis is contraindicated.

We considered early invasive ventilation to improve the balance between oxygen delivery and utilisation, because of the high work of breathing secondary to the severe metabolic acidosis. Although she was elderly, she could still hyperventilate to balance the acidosis. Before starting mechanical ventilation, we hoped to improve her metabolic situation with bicarbonate and CVVH, because we suspected deepening of the acidosis immediately after commencing mechanical ventilation. In our experience, spontaneous ventilation will usually better balance metabolic acidosis than mechanical ventilation will.

To assess the intestinal complications and extent of this formalin intoxication, we decided to perform a gastroduodenoscopy. Before performing this investigation, we discussed whether or not she would benefit from this diagnostic procedure, since it could harm her because of a possible perforation of her gastrointestinal tract and possible aspiration. She did not undergo this procedure earlier because it was thought she only had a minor intoxication at presentation, but this procedure was still performed well within the first 24 hours as recommended.[11] We decided to perform this gastroscopy not only to investigate the extent of the formalin intoxication, but also to be able to insert an enteral feeding tube to prevent stricture of her oesophagus. Furthermore, we started early enteral feeding to preserve the enteric mucosa. As described earlier, after oral intake of formalin, in general the stomach suffers the most. This was established in our patient too. Although she developed necrosis of the stomach, no signs of perforation were seen on the abdominal CT, nor signs of intestinal perforation later on in the clinical course. Since it is recommended to start gastric acid inhibitory therapy,[7] we decided to start proton pump inhibitory therapy (pantoprazole 2 dd 40 mg iv). We also started antibiotic therapy not only because we use selective intestinal decontamination therapy, but also to treat a possible secondary bacteraemia because of suspected intestinal lesions due to the caustic effects of the formalin and the suspected intestinal ischaemia secondary to her severe shock.

We have described a case of an elderly woman with not only local damage to the intestinal mucosa due to a formalin intoxication, but also severe metabolic acidosis and multiple organ failure. Although the literature suggests that (high-dose) formalin intoxications are often fatal,[1-6] our patient survived. This is probably due to the small amount she used unintentionally (approximately 1080 mg of formaldehyde and 480 mg of methanol) as well as our intensive treatment approach (folinic acid (1 mg/kg every 4 hours), dialysis and ICU management for multiple organ failure). Even low-dose formalin intoxications should therefore be seen as serious intoxications.

Disclosures

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