BMJ Case Rep. 2009; 2009: bcr09.2008.1013.
Published online 2009 April 7. doi: 10.1136/bcr.09.2008.1013
PMCID: PMC3029121

Learning from errors

Keeping a high index of suspicion: lessons learned in the management of methanol ingestion

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Abstract

Methanol ingestion is an uncommon form of poisoning that can cause severe metabolic disturbances and potentially fatal and often irreversible organ/tissue damage. The diagnosis is sometimes elusive and requires a high index of suspicion. Because extent and irreversibility of the damage caused by formic acid is time sensitive, methanol poisoning should be recognised promptly so that it can be treated. Metabolic acidosis associated with an increased anion gap and osmolar gap is an important laboratory finding but is not always present. A case of severe methanol poisoning is presented that demonstrates the unique challenges in the diagnosis and management, and the lack of readiness of the health care system for such cases. We highlight some of the diagnostic difficulties associated with treating a patient with a reduced level of consciousness and severe metabolic acidosis. We also review the pitfalls of using laboratory tests to rule out alcohol ingestion and discuss the definitive management of methanol poisoning.

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BACKGROUND

Diagnosis of methanol toxicity is not always straightforward,[1] and it requires a high index of suspicion. Unfortunately, the early findings, including nausea, vomiting, and altered mentation, are non-specific. It is important to emphasise that the onset of methanol toxicity is delayed when ethanol is co-ingested. Methanol is absorbed well in the gastrointestinal tract, with peak values attained in 30–90 min. The serum half-life ranges from 14 to 20 h. Toxicity results from the formation of formic acid through the action of hepatic alcohol dehydrogenases (fig 1). Further metabolism of formic acid to carbon dioxide is dependent on folate. The minimal lethal dose of methanol is not yet known. Delay in initiating antidote treatment corresponds to an increased conversion of methanol

to formic acid, which is responsible for the potentially fatal and often irreversible organ/tissue damage.

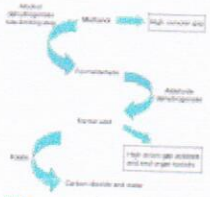

Figure 1
Methanol metabolism.
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CASE PRESENTATION

Case history and hospital course

A previously healthy middle aged man was brought unconscious to the emergency department by his family. They reported that he had been drowsy all day, complaining of blurred vision, headache, and vomiting. He was later found unconscious in his room with frothy oral secretions. He had no history of head injury, fever, or abnormal jerky movements and no past history of hypertension, cardiac disease, diabetes, or seizures. On arrival at the emergency department, he was unresponsive and flaccid, with fixed dilated pupils. His blood pressure was 72/36 mm Hg with a pulse rate of 32 beats/min. No trauma or needle marks were found.

Investigations

On arrival at the emergency department, the patient was intubated, ventilated, and resuscitated. He required large volumes of fluids and maximum inotropic support to maintain vital signs. He was then given activated charcoal. Because there was no intensive care bed available, the patient was kept in the emergency department throughout his hospital stay. The initial blood count, troponin concentrations, and chest *x* ray findings were normal, and brain computed tomography (CT) showed no abnormalities. The prothrombin time was 20 s, the international normalised ratio (INR) was 1.7, and the partial prothrombin time was 60 s. Random blood glucose concentrations were 11.7 mmol/l. Arterial blood gas findings were as follows: pH 6.52, Pco_2 58.2 mm Hg, Hco_3 4.5 mmol/l, and oxygen saturation 98% on 100% oxygen. Serum electrolytes were as follows: Na 138 mmol/l, K 4.5 mmol/l, and Cl 99 mmol/l. His urea was 7 mmol/l.

The anion gap was 34.5 mmol/l, and the calculated osmolality was 294.7 mOsm/kg. The measured osmolality was 301 mOsm/kg to give and osmolality gap of 7 mOsm/kg which fit within the normal range (±10 mOsm/kg).

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TREATMENT, OUTCOME AND FOLLOW-UP

In the emergency department the patient had several short seizures, which were controlled with diazepam and phenytoin. Methanol poisoning was suspected because of the patient's presentation, with altered level of consciousness and the presence of very high anion gap acidosis; however, the methanol level could not be confirmed biochemically because the analysis was not available in our hospital. Ethanol infusion could not be started until the second day, because intravenous ethanol was not available. The patient underwent haemodialysis on day 2 of hospitalisation. He remained unstable, with persistent severe metabolic acidosis despite maximal haemodynamic support. He experienced three cardiopulmonary arrests and could not be revived from the third (on day 3). A history of ingestion of a large amount of locally made perfume with high methanol concentration was obtained on the third day from a close friend of the patient.

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DISCUSSION

Clinical features

The onset of symptoms is associated with accumulation of the toxic metabolite formic acid, which leads to inhibition of mitochondrial respiration, hypoxia, and lactate formation. Onset of signs and symptoms ranges from 30 min to more than 30 h post-ingestion, depending on the amount of methanol ingested, whether ethanol has also been ingested, accumulation of formic acid, the patient's underlying folic acid stores, and individual variations in response.[2]

Physicians should not assume insignificant ingestion, because the clinical presentation can range from a few symptoms and signs to full toxicity, depending on the amount of accumulated formate.

The main systems involved in methanol toxicity are the neurologic, gastroenterologic, and ophthalmologic systems. Tachycardia, tachypnoea, and hypotension are common manifestations in severe cases and indicate metabolic acidosis. Hypotension and bradycardia, when present, are preterminal findings.[3,4]

Central nervous system symptoms relate to the concentration of formic acid that has built up. Patients are often alert on presentation. Depressed mental status, confusion, and ataxia are not uncommon manifestations. In severe cases, coma and seizures may be noted.[2] Magnetic resonance imaging and/or CT of the brain may reveal basal ganglia infarcts consistent with parkinsonian syndrome, which has been reported after methanol poisoning.[5,6]

Eye involvement is seen in approximately 50% of patients and is associated with high methanol concentration. Signs and symptoms may develop 6 h or more post-ingestion but

can be delayed 24 h or more. Eye symptoms include: blurred vision; photophobia; visual hallucinations, such as "a snowstorm," partial to total visual loss; and, rarely, eye pain. Eye examination findings range from normal to visual field constriction, sluggish non-reactive pupils, nystagmus, hyperaemic optic discs, papilloedema, retinal oedema and haemorrhages, and decreased to absent vision. The most common acute field defect is a dense central scotoma.[7]

Nausea and vomiting are common gastrointestinal symptoms. Other manifestations include flank pain, abdominal pain that is often severe from mucosal irritation, gastrointestinal haemorrhage, diarrhoea, liver function abnormalities, and pancreatitis.[2]

Outcome is best correlated with the severity of the acidosis rather than with serum methanol concentrations. Coma or seizures at presentation and a serum pH <7.0 were found to be the factors most closely correlated with death.[8]

Laboratory investigations

Serum methanol concentrations are usually determined by gas chromatography, but this technique is not widely available and samples frequently must be sent to a reference laboratory.

Calculating the osmolar gap does not permit differentiation among ethanol, isopropyl alcohol, methanol, and ethylene glycol.[10] The molar quantity of uncharged molecules is estimated, and therefore the osmolar gap increases only in the presence of the parent alcohols. Although an increased osmolar gap is usually present in cases of serious methanol ingestion, methanol poisoning with a normal osmolar gap may be seen. The toxic acid metabolite of methanol (formate) does not contribute to the calculated osmolar gap. As a result, the osmolar gap is an insensitive tool in late presentations, because most of the methanol has been metabolised. An unexplained, large osmolar gap is presumptive evidence of recent methanol exposure.[9,10] The higher the osmolar gap, especially if >20 mOsm/l, the more specific it is for the presence of an alcohol.

A widened anion gap should be evaluated, because it is a common finding in methanol intoxication. If the anion gap is unexplained and other possible causes have been excluded, the methanol concentration should be measured. Metabolic acidosis associated with an unexplained widened anion gap may be considered an indication for empiric treatment for toxic alcohol poisoning, pending definitive diagnosis. An elevated osmolar gap with a concomitant increased plasma anion gap (which is not explained by ethanol ingestion) mandates examination of serum for methanol and ethylene glycol.

Management

To avoid morbidity resulting from delay, emergency physicians must often make treatment decisions without definitive serum drug values, based only on clinical suspicion and readily available laboratory data. The general measures involved in treatment are supportive care, correction of acidosis, administration of fomepizole or ethanol to

decrease conversion to toxic metabolites, and dialysis to eliminate the methanol.[9] Gastric lavage is unlikely to be of benefit. Unfortunately, given the rapid absorption of methanol, unless ingestion has occurred within 1 h before presentation, administration of activated charcoal is probably not useful.[11]

Supportive care

Supportive care includes intubation if the patient is unconscious or if there is any concern about maintaining an airway and ventilation. Rapid sequence intubation in experienced hands remains the method of choice for intubation in intoxicated patients. Intravenous normal saline administration should be started immediately in all patients with signs of decreased perfusion, including but not limited to hypotension, increased capillary refilling time, cold clammy skin, and decreased urine output. $NaHco_3$ 1 mEq/kg intravenously should be started for severe acidosis if the serum pH falls below 7.2. Massive amounts may be necessary.

Fomepizole treatment

Fomepizole should be started when the methanol concentration is >20 mg/dl, ingestion is >0.4 mg/kg, or pH is <7.15. Fomepizole is administered at a loading dose of 15 mg/kg, followed by 10 mg/kg every 12 h for a total of four doses. Each of these four doses is given by slow intravenous infusion over 30 min. Dosing every 4 h is required during haemodialysis because fomepizole is removed during the procedure.[12,13]

Ethanol administration

Ethanol is indicated for patients with a known fomepizole allergy or when fomepizole is not readily available. Intravenous administration is preferred. The intravenous solution should contain 10% ethanol in D5W, with a loading dose of 10 ml/kg and maintenance at 1.5 ml/kg/h to maintain a concentration of 100–150 mg/dl.[3] If dialysis is initiated, a higher maintenance infusion will be necessary, because ethanol is dialysable.

Cofactor therapy

Because degradation of formic acid to carbon dioxide (fig 1) is folate dependent in methanol intoxication,[14] all patients with methanol poisoning should also receive cofactor therapy: either folinic acid 50 mg intravenously or folic acid 50 mg intravenously every 6 h.[9,15]

Dialysis

The indications for dialysis in cases of confirmed methanol overdose include metabolic acidosis, renal compromise, visual symptoms, and serum methanol concentrations above 20 mg/dl.[16] Dialysis and fomepizole or ethanol are continued until values are zero and acidosis has resolved.

LEARNING POINTS

- The practice of categorically ruling out methanol exposure on the basis of an normal osmolar gap is unjustified, as is assuming that a small elevation of the osmolar gap in a patient with a low pre-test probability is due to a toxic alcohol.
- Methanol poisoning should be considered in patients with altered mental status, visual complaints, or metabolic acidosis associated with a high anion gap and/or osmolar gap.
- Emergency physicians should start treatment for suspected methanol intoxication without delay, without waiting for confirmation of the methanol concentration.

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Footnotes

Competing interests: none.

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