Alcohols and glycols

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Abstract

Ethanol is a central nervous system depressant and a peripheral vasodilator, thereby causing coma, hypothermia and hypotension in severe poisoning. Hypoglycaemia, particularly in children, is observed together with acid–base disturbances, which are common (respiratory acidosis is observed more frequently than metabolic acidosis, and metabolic alkalosis may be observed in those vomiting and hypovolaemic). Lactic acidosis (usually mild) is an uncommon but potentially serious complication. Haemodialysis may be considered if the blood ethanol concentration exceeds 7500 mg/L and severe metabolic acidosis is present.

The principal features of severe methanol poisoning are metabolic acidosis and blindness. The first priority of management is to inhibit methanol metabolism using either intravenous fomepizole or ethanol. In addition, sodium bicarbonate and folinic acid should be administered to correct acidosis and increase formate metabolism respectively. Haemodialysis will enhance methanol and formate elimination and correct acid–base disturbances.

Diethylene and ethylene glycols are both metabolized by alcohol and aldehyde dehydrogenases to produce toxic metabolites. Both glycols produce coma, seizures, metabolic acidosis and renal failure, though by different mechanisms. Management involves the administration of fomepizole or ethanol to prevent metabolism of the glycol, correction of acidosis, and the use of haemodialysis to remove the glycol and metabolites.

Keywords acid–base disturbances; blindness; cranial nerve palsies; diethylene glycol; ethanol; ethylene glycol; fomepizole; metabolic acidosis; methanol; renal failure

Ethanol

Ethanol (alcohol, ethyl alcohol) is widely available as a beverage, is an important constituent of cosmetics, aftershave, hair tonic, antiseptics, mouthwashes, dishwashing detergents and glass cleaners, and is commonly used as an industrial solvent.

Acute ethanol poisoning is an uncommon cause of adult death; when fatalities occur, aspiration of gastric contents is an important factor. More often, ethanol potentiates the effects of other drugs taken in overdose. However, ethanol intoxication is an important cause of accidental death in children under 5 years of age. Children may be forced to drink alcohol under duress, and this may be associated with sexual abuse. In young children who have not eaten for 8–12 hours, ingestion of even modest amounts of ethanol (e.g. the dregs left after a party) can lead to permanent neurological damage as a result of hypoglycaemia.

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Toxicokinetics

Ethanol is absorbed rapidly through the gastric and small intestinal mucosae.[1] Peak blood ethanol concentrations usually occur within 30–90 minutes of ingestion. Gastric alcohol dehydrogenase isoenzyme has a role in metabolizing ethanol before absorption,[2,3] thereby preventing ethanol entering the systemic circulation, particularly following ingestion of moderate amounts of alcohol. Younger women[4] and ethanol abusers of both sexes,[2] have lower gastric alcohol dehydrogenase activity than younger and non-abusing men; therefore, more ethanol is absorbed in these individuals and higher blood alcohol concentrations ensue.

Absorbed ethanol is initially and principally converted to acetaldehyde by a nicotinamide adenine dinucleotide (NAD)-dependent hepatic alcohol dehydrogenase.[1] A small proportion is oxidized by the microsomal ethanol-oxidizing system (MEOS)[1] and the catalase pathway. MEOS activity may be increased by chronic alcohol abuse and by enzyme-inducing drugs[1]; this may explain the greater ethanol tolerance seen in heavy drinkers. Acetaldehyde, which is toxic, is removed by oxidation via the (oxidized) NAD-dependent enzyme, aldehyde dehydrogenase, to yield acetate and, subsequently, carbon dioxide and water.[1]

About 95% of ingested ethanol is oxidized to acetaldehyde and acetate; the remainder is excreted unchanged in the urine (at a concentration about 1.3 times more than that in the blood), and, to a lesser extent, in the breath (the blood:breath ratio is about 2300:1) and through the skin.

At high blood concentrations (>1000 mg/L) ethanol is eliminated by zero-order kinetics (i.e. the rate of elimination is constant regardless of concentration), so that ethanol concentrations can be expected to decrease at a constant rate of 60–400 mg/L/hour (usually 150 mg/L/hour). Regular social drinkers tend to have higher ethanol elimination rates than non-drinkers, but ethanol abusers with severe liver damage usually eliminate ethanol more slowly.

Mechanisms of toxicity

Ethanol is a central nervous system (CNS) depressant[5] that interferes with cortical processes in small doses and may depress medullary function in large doses. The effects of ethanol on the CNS are generally proportional to the blood ethanol concentration, though the precise mechanisms of toxicity responsible for these effects are not yet fully understood. Individuals who are habituated to ethanol may have few symptoms despite massive blood ethanol concentrations. In contrast, teenagers unaccustomed to ethanol may become comatose at more modest blood ethanol concentrations (1000–2000 mg/L).

Ethanol is also a peripheral vasodilator. In the severely intoxicated, it may cause hypothermia and hypotension.

Ethanol metabolism may result in accumulation of free reduced nicotinamide adenine dinucleotide (NADH), with a resultant increase in the NADH:NAD ratio[6] and inhibition of hepatic gluconeogenesis. It can also cause an increase in the lactate:pyruvate ratio, with development of hyperlactataemia. Inhibition of hepatic gluconeogenesis may result in hypoglycaemia,[7] particularly in children or when poisoning follows fasting, exercise or chronic malnutrition.

Features

These are summarized in Table 1. Typically, ethanol-induced hypoglycaemia occurs within 6–36 hours of ingestion of

Features of acute ethanol intoxication related to blood ethanol concentrations

<500 mg/L — mild inebriation
- Talkativeness, subjective feeling of well-being

500–1500 mg/L — mild poisoning
- Emotional ability and slurred speech
- Mild impairment of visual acuity, muscular coordination and reaction time

1500–3000 mg/L — moderate poisoning
- Blurred vision
- Loss of sensory perception
- Incoordination
- Ataxia
- Slowed reaction time

3000–5000 mg/L — severe poisoning
- Marked incoordination
- Blurred or double vision
- Sometimes coma and hypothermia
- Occasionally hypoglycaemia and convulsions

≥ 5000 mg/L — very severe poisoning
- Coma
- Respiratory depression
- Depressed reflexes
- Hypotension and hypothermia
- Death may occur from respiratory or circulatory failure, or as a result of aspiration of stomach contents in the absence of a gag reflex

Table 1

a moderate-to-large amount of ethanol by a previously malnourished individual or one who has fasted for the previous 24 hours; it is common in children up to 5 years of age. The patient is often comatose, hypothermic and convulsing, with conjugate deviation of the eyes, trismus and extensor plantar reflexes; the usual features of hypoglycaemia (e.g. flushing, sweating, tachycardia) are often absent. Convulsions are the most common presenting sign in children with hypoglycaemia.

Acid–base disturbances are common in acute ethanol poisoning.[8] Respiratory acidosis is commoner than metabolic acidosis,[9] and metabolic alkalosis is observed in those vomiting and hypovolaemic.[8] In some studies the magnitude of the metabolic acidosis did not correlate well with the blood ethanol concentration or the lactate concentration,[10] whereas in others the correlation was good.[11] Lactic acidosis (usually only mild) is an uncommon but potentially serious complication of acute ethanol intoxication, and occurs particularly in patients with severe liver disease, pancreatitis or sepsis. Hypovolaemia, which may accompany severe intoxication, predisposes to lactic acidosis.

Management

Supportive measures are all that are required for most patients with acute ethanol intoxication, even if the blood ethanol concentration is very high. Particular care should be taken to protect the airway. In more severe cases, acid–base status should be determined every two hours; this may be performed conveniently on a venous sample, unless the patient is hypotensive.

Management of lactic acidosis requires correction of hypoglycaemia, hypovolaemia and circulatory insufficiency, if present. An infusion of sodium bicarbonate will be necessary in those patients in whom a lactic acidosis persists.

Blood glucose should be determined hourly and the rate of intravenous glucose adjusted accordingly. If blood glucose concentrations decrease despite an infusion of glucose 5–10%, a 50% solution (50 mL intravenously) should be given because hypoglycaemia is usually unresponsive to glucagon.

Haemodialysis[12] may be considered if the blood ethanol concentration exceeds 7500 mg/L and if a severe metabolic acidosis is present, which has not been corrected by the measures outlined above.

Fructose is of negligible clinical benefit in accelerating ethanol oxidation and may cause acidosis[13]; it should not be used. In chronic alcohol abusers it is important to replace thiamine intravenously initially to reduce the risk of Wernicke-Korsakoff syndrome developing.

Methanol

Methanol is found in antifreeze solutions and windscreen-washing fluid and is used widely as a solvent and to denature ethanol. Ingestion of as little as 10 mL of pure methanol has caused permanent blindness and 30 mL is potentially fatal.

Mechanisms of toxicity

Methanol itself has a relatively low toxicity, but produces toxic metabolites (Figure 1).[14,15] Formic acid accumulates and there is a direct correlation between its concentration and toxicity.[16–18] The acidosis observed appears to be caused directly or indirectly by formic acid production.[14,19] Formic acid has also been shown to inhibit cytochrome oxidase[20] and is the principal cause of ocular toxicity,[21,22] though acidosis can increase toxicity further by enabling greater diffusion of formic acid into cells.

Features

Methanol causes mild and transient inebriation, nausea, vomiting, abdominal pain and mild CNS depression. This is followed by a latent period of 12–24 hours after which uncompensated metabolic acidosis develops (the mortality increases with the severity and duration of the acidosis),[15,22] coma supervenes[22] and visual function becomes impaired[15]; this ranges from blurred vision and altered visual fields to complete blindness.[21] Hyperglycaemia and raised serum amylase activity[23] may ensue. Patients who survive may suffer permanent neurological sequelae, including blindness, rigidity, hypokinesis and other parkinsonian-like signs.[24] Respiratory arrest, coma and severe metabolic acidosis are strong predictors of poor outcome.[25]

Management

Supportive measures should be employed and metabolic acidosis should be treated conventionally. If presentation is early after exposure, the first priority is to inhibit methanol metabolism using either intravenous fomepizole[14,26,27] or ethanol.[14,22] Fomepizole requires less monitoring, but is more expensive than ethanol.