Methanol and Ethylene Glycol Poisonings
Mechanism of Toxicity, Clinical Course, Diagnosis and Treatment

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Summary

Methanol and ethylene glycol poisonings share many characteristics both clinically and biochemically. Both alcohols are metabolised via alcohol dehydrogenase to their toxic metabolites. Methanol is slowly metabolised to formaldehyde which is rapidly metabolised to formate, the metabolite mainly responsible for methanol toxicity. Formate metabolism depends upon the folate pool which is small in primates compared with other animals. Therefore, formate accumulates in primates during methanol intoxication and is mainly responsible for the metabolic acidosis in the early stage of intoxication. In late stages lactate may also accumulate, mainly due to formate inhibition of the respiratory chain. This tissue hypoxia caused by formate may explain the ocular as well as the general toxicity.

Ethylene glycol is metabolised more rapidly than methanol, via alcohol dehydrogenase to glycolaldehyde which is rapidly metabolised to glycolate, the metabolite mainly responsible for the metabolic acidosis in ethylene glycol poisoning. Glycolate is metabolised by various pathways, including one to oxalate which rapidly precipitates with calcium in various tissues and in the urine. Ethylene glycol toxicity is complex and not fully understood, but is mainly due to the severe metabolic acidosis caused by glycolate and to the calcium oxalate precipitation.

The clinical course in both poisonings is initially characterised by the development of metabolic acidosis following a latent period, which is more pronounced in methanol poisoning and is the time taken for both alcohols to be metabolised to their toxic metabolites. In methanol poisoning there are usually visual symptoms progressing to visual impairment, whereas ethylene glycol victims develop renal and cardiopulmonary failure.

Prognosis is excellent in both poisonings provided that there is early treatment with alkali to combat acidosis, ethanol as an antimetabolite, and haemodialysis to remove the alcohols and their toxic metabolites. Ethanol is also metabolised by alcohol dehydrogenase, but has a much higher affinity for this enzyme than methanol and ethylene glycol. Presence of ethanol will therefore inhibit formation of toxic metabolites from methanol and ethylene glycol. Due to competition for the enzyme, the therapeutic ethanol concentration depends on the concentration of the other two alcohols, but a therapeutic ethanol concentration around 22 mmol/L (100 mg/dl) is generally recommended.

Most patients are, however, admitted at a late stage to hospitals not capable of performing analyses of these alcohols or their specific metabolites on a 24-hour basis. Treatment is therefore often delayed because of delayed diagnosis, with fatal consequences. In situations where specific analyses are not available, the calculation of the anion and osmolar gaps in every case of metabolic acidosis of unknown origin can provide the diagnosis, allowing treatment to be started earlier. In ethylene glycol poisonings urine micro-
Methanol (methyl alcohol, 'wood-alcohol', 'carbinol', 'colonial spirit') is a colourless, volatile and easily flammable liquid. It has its own weak, peculiar smell but this is often difficult to recognise in the mixed liquids causing the poisonings. Methanol is produced in large quantities industrially by the catalytic reaction of carbon monoxide or dioxide with hydrogen, and is used in the production of formaldehyde and methylated compounds, e.g. methylesters. Methanol is also widely used as a solvent in different industries and laboratories. The proposed introduction of methanol as an alternative fuel resource will expose far more people to this substance which may lead to an increase in acute poisonings. Methanol poisoning currently occurs with low frequency but, when it does occur, many people are often involved, giving this poison a special place within the field of clinical toxicology (Bennett et al. 1953; Naraqi et al. 1979). The mechanism of toxicity, the well defined clinical course, the possibility of treatment and the fatal course without treatment further emphasise this special place. The lethal dose of methanol given in the literature varies from 30 to 240ml but according to Roe (1982) it seems reasonable to regard 1 g/kg as the minimum lethal dose in man. The minimum dose causing permanent visual defects is unknown.

Ethylene glycol shares many clinical and biochemical characteristics with methanol. Therefore, poisoning with both compounds is discussed in this paper. In fact, in recent times ethylene glycol poisoning has been more common than methanol poisoning, but the former usually lacks the aspect of mass-poisoning. The mechanism of the toxicity of ethylene glycol is less well understood than that of methanol, probably because of the smaller amount of research information. Ethylene glycol is best known as an antifreeze in internal combustion engines, but it is also used as a solvent and for various manufacturing processes. As with methanol, the lethal dose of ethylene glycol given in the literature varies considerably, with about 100ml (adults) as the most frequently cited approximation.

1. Mechanism of Toxicity

1.1 Methanol

Clinical observations of methanol-poisoned patients reveal a characteristic delay (generally 12 to 24 hours) before the onset of symptoms and development of metabolic acidosis (Bennett et al. 1953; Roe 1946). Furthermore, there is no relationship between the blood concentration of methanol and the degree of toxicity. These observations suggest that a metabolite of methanol is the principal toxic agent rather than methanol itself. However, identification of the toxic metabolite(s) has been delayed because experimental studies have been performed in non-primate animals, which do not develop acidosis or symptoms of poisoning when exposed to methanol (Hunt 1902; Roe 1955). The methanol toxicity pattern in these animals is more like that of a narcotic than an acidic nature. The difficulties in identifying appropriate animal models hampered the study of methanol toxicity until it was demonstrated that rhesus and pigtail monkeys represent a useful model for this purpose (Clay et al. 1975; Gilger & Potts 1955; Martin-Amat et al. 1977; McMartin et al. 1975). The administration of methanol to monkeys (at 3 g/kg) produces few signs or symptoms for 8 to 12 hours, but severe metabolic acidosis, ocular toxicity, coma, and death develop if no treatment ensues. Studies of the effects of 4-methylpyrazole (4MP), an inhibitor of alcohol dehydrogenase and hence methanol metabolism, in the monkey, con-