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Clinical and Forensic Toxicology of Methanol

A. W. Jones

Division of Drug Research
Department of Biomedical and Clinical Sciences
Linköping University
Linköping, Östergötland
Sweden

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* Contact information: Dr. A. Wayne Jones, Division of Drug Research, Department of Biomedical and Clinical Sciences, Linköping University, 581 85 Linköping, Sweden; wayne.jones@liu.se.

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ABSTRACT: Methanol has a very simple chemical structure (CH_3OH) considering its potential health hazard, including the many poisoning deaths after ingestion. In countries where authentic alcoholic beverages are expensive, restricted, or banned for religious or other reasons, some people resort to purchasing alcoholic drinks made illegally. These clandestine sources of "booze" often contain high concentrations of methanol, added by the perpetrators to enhance potency and increase profits. Although an effective medical treatment for methanol poisoning exists, because most such incidents occur in socially deprived parts of the world, the hospital emergency facilities are scarce and/or inadequate.

Trace amounts of methanol (median ~1.0 mg/L) are produced endogenously via certain enzymatic processes, such as one-carbon metabolism. Methanol and methyl esters are also contained in fresh fruits and vegetables as well as in alcoholic beverages. During a period of heavy drinking the blood-methanol concentration (BMC) increases and might surpass 10 mg/L, which is considered a biomarker for alcohol abuse and alcoholism.

Methanol itself has a low intrinsic toxicity, but is converted in the body into two highly toxic metabolites, formaldehyde and formic acid. This metabolism is delayed by co-ingestion of ethanol, which creates a latent period of 12–24 h before toxic symptoms develop. Accordingly, when patients are admitted to hospital for diagnosis and treatment, a life-threatening metabolic acidosis has already developed and is irreversible. Symptoms of methanol poisoning include blurred vision, breathlessness, nausea, gastric pains, and acid-base disturbances and deficiency of oxygen in arterial blood. The visual disturbances might even develop into permanent blindness, owing to an interaction of toxic metabolites with the optic nerve. The minimum lethal dose of ethanol in humans is not easy to specify, because most poisonings involve co-ingestion of ethanol, which to some extent protects the patient from toxic sequelae.

Effective antidotes for treatment of methanol poisoning are administration of ethanol or the therapeutic drug fomepizole (Antizol®), which is 4-methyl pyrazole (4-MP). Both treatments work by blocking the metabolism of methanol by liver alcohol dehydrogenase (ADH). The metabolic acidosis caused by the accumulation of formic acid in the body is treated with sodium bicarbonate, which helps to normalize pH in the bloodstream. Thereafter, methanol and its metabolites in the blood are removed by hemodialysis. However, the long-term prognosis for survivors of methanol poisoning is not good, because many are elderly males who are in poor health and often suffer from an alcohol-use disorder.

KEYWORDS: Alcohol, antidotes, clandestine spirits, ethanol, human health, methanol, treatment of poisoning, toxic alcohols.

INTRODUCTION

Compared with ethanol, which is the alcohol contained in beer, wine, and distilled spirits, the closely related aliphatic alcohol, methanol (wood alcohol), is much more dangerous to human health [124,173]. Outbreaks of methanol poisoning predominantly occur in economically deprived nations, where people are more tempted to purchase illegally produced cheaper alcoholic drinks [3,4]. Conventional alcoholic drinks might be scarce, or banned for religious or other reasons, and a black market has emerged for the manufacture and sale of counterfeit alcoholic drinks [163]. Unscrupulous individuals fortify home-brewed "booze" with methanol to boost their profits and this practice has resulted in many poisoning deaths. The pharmacological effects of ethanol and methanol are similar, because both alcohols act as depressants of the central nervous system and initially intoxicating effects are hard to distinguish [188].

Methanol itself is not particularly dangerous, but once absorbed into the bloodstream it is rapidly converted in the liver into two toxic metabolites, namely formaldehyde and formic acid [96]. Formaldehyde is a highly reactive chemical species and binds to amino acids and proteins, which might cause altered membrane signaling or enzyme activity [183]. Formic acid is a strong organic acid (pKa 3.77) that easily crosses the blood-brain barrier and interacts with the optic nerve; hence, visual disturbances and permanent blindness are common sequelae [46,81]. The formic acid metabolite is also responsible for disrupting acid-base homeostasis in the body, lowering pH in the blood and causing a life-threatening metabolic acidosis, respiratory failure, and death [91,99,123].

This article presents a review of the chemistry and pharmacology of methanol, including its endogenous synthesis and concentrations determined in blood of healthy abstaining subjects with and without concomitant ingestion of ethanol. The disposition and fate of methanol in the body are reviewed, as are studies of its pharmacokinetics in moderate drinkers and alcoholics. Finally, the epidemiology of mass poisonings with methanol is highlighted, including the typical symptoms and the most effective treatment options.

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ABOUT THE AUTHOR

A. W. Jones

Alan Wayne Jones received both a B.Sc. in chemistry (1969) and a Ph.D. (1974) from the University of Wales (Cardiff, UK). Dr. Jones retired in 2013 from his appointment as a senior scientist at Sweden's National Laboratory of Forensic Medicine, Division of Forensic Genetics and Forensic Toxicology (Linköping, Sweden). He is currently a guest professor in forensic toxicology at the Division of Drug Research, Department of Biomedical and Clinical Sciences, University of Linköping, Sweden.

Although Professor Jones was born and educated in the UK, he has spent most of his career working in Sweden. His doctoral thesis was entitled *"Equilibrium Partition Studies of Alcohol in Biological Fluids"* and dealt with analytical and physiological aspects of ethanol determination in blood and exhaled breath-samples. In 1993 Dr. Jones applied for and was awarded a senior doctorate degree (D.Sc.) by the University of Wales for his body of published work in experimental alcohol research and toxicology of ethanol and other drugs of abuse.

Dr. Jones has lectured widely on forensic aspects of alcohol at home and abroad and has testified as an expert witness in hundreds of criminal trials involving drug-related crimes in Sweden as well as the United States, the United Kingdom, Denmark, Norway, Ireland, and New Zealand. Since 1978 Dr. Jones has had considerable experience as a peer-reviewer of scientific articles and he has served on editorial boards of several international journals devoted to substance abuse, analytical toxicology, the forensic sciences, and legal medicine. Since his first publication in 1974, Dr. Jones's bibliography now lists some 450 articles, most of which have appeared in peer-reviewed journals. Mostly as a single author, Dr. Jones has written scores of book chapters and has contributed to several encyclopedias about forensic sciences, legal medicine, and analytical toxicology.

In recognition of his many contributions to research and scholarship, Dr. Jones received peer recognition with a Widmark Award (1997) from the International Council on Alcohol, Drugs and Driving (ICADTS), the Rolla Harger Award (2002) from the American Academy of Forensic Sciences (AAFS), the Robert Borkenstein Award (2004) from the US National Safety Council, the Alan Curry Award (2011) from The International Association of Forensic Toxicologists (TIAFT), and most recently the Kurt Dubowski Award (2017) from the International Association of Chemical Testing (IACT).