Methanol

CAS: 67-56-1
MF: CH_4O
MW: *32.04*
log Kow= -0.77
pKa = 15.3
Solubility: Soluble in acetone and chloroform. Miscible with water, ethanol, ether, benzene, most organic solvents and ketones [1].

Major uses
Methanol is widely used in paint, varnish removers and as an industrial solvent. It is the raw material for making formaldehyde and methyl esters of organic and inorganic acids. It is used as antifreeze for automotive radiators and brakes; ingredient of gasoline and diesel oil antifreezes and as octane booster in gasoline. Furthermore, it is used as fuel for picnic stoves and soldering torches, for extracting animal and vegetable oils, to denature ethanol, softening agent for pyroxylin plastics, and as solvent and solvent adjuvant for polymers as well as solvent in the manufacture of cholesterol, streptomycin, vitamins, hormones, and other pharmaceuticals [1, 2].

Human toxicity
Methanol is highly toxic, producing metabolic acidosis, blindness, and death. Toxicity is related to the degree of acidosis and thus the time between exposure and specific treatment. Prognosis is poor in patients with coma or seizure and severe metabolic acidosis (pH <7). Most exposures to methanol result from ingestion; however, symptoms may also occur from inhalation, skin absorption or intravenous injection [2].

Acute poisoning causes initial drowsiness, confusion and ataxia. These symptoms are similar to mild ethanol inebriation. Because methanol must be metabolized, additional clinical signs and laboratory findings of metabolic acidosis may be delayed for 18 to 24 hours. Then the patient may experience nonspecific malaise, headache, vomiting, abdominal pain, nausea, vomiting, and visual changes. If untreated, methanol poisoning progresses to coma, metabolic acidosis due to the accumulation of the toxic metabolite formic acid, and finally respiratory or circulatory arrest and death [2].

The most common permanent effects following severe poisoning are optic neuropathy, blindness, Parkinsonism, toxic encephalopathy, and polyneuropathy [2].

Lethal symptoms: CNS depression, metabolic acidosis, cardiovascular failure.

Serious toxicity may occur from ingestion of 0.25 ml/kg of 100 percent methanol. Fatalities might occur from ingestion of 0.5 ml/kg of 100 percent methanol. Mortality is related to the time interval between exposure and the institution of specific therapy [2]. In the absence of medical treatment, the minimum lethal dose of methanol is between 0.3 and 1 g/kg. An amount of 100 - 200 ml is fatal to most adults. Ingestion of less than 30 ml has been reported to cause death [2].

Blood methanol levels greater than 25 mg/dl (8 mmol/l) are generally considered toxic. A plasma methanol concentration of about 40 mg/dl has been fatal in humans, but there is a wide variation in individual sensitivity. A peak serum methanol level of

920 mg/dl was reported in a patient who ingested 500 ml methanol in a suicide attempt and survived [2].

Working place standards [2]:
TLV-TWA: 200 ppm
TLV-STEL: 250 ppm

Kinetic data
Absorption: Methanol is rapidly absorbed through the skin, respiratory tract and gastrointestinal tract [2].

Volume of distribution: 0.6 l/kg [2, 3].

Time to peak: Peak plasma levels are usually reached within 30 to 60 minutes following ingestion, although a long latent period (roughly 18 to 24 hours) usually is seen before toxic symptoms develop [2,3].

Distribution:
Methanol is distributed in the body water, like ethanol, to an extent of about 50% to 60% of the body weight. Methanol passage the blood-brain barrier freely [3]. Methanol is practically insoluble in body fat, however, and it is found in higher concentrations in the ocular fluids, cerebrospinal fluid, and gastric secretions [2]. It accumulates especially in liver and kidney [3].

Tissue distributions of methanol in a man found dead after ingestion of an unknown amount of methanol included blood methanol level of 142 mg/dl, tissue/fluid levels (mg/100 g) were: bile - 175; vitreous - 173; brain-159; kidney - 130; lung - 127; spleen - 125; muscle - 125; liver - 107; and heart - 93.

The plasma half-life: 2.4-3.2 hours [2]. At overdoses plasma half-life of around 25 hours (range 20 to 29) has been reported [3]. Hemodialysis reduced the half-life of methanol in the body from 8 to 2.5 hours [2]. Zero-order elimination of methanol with a rate of 8.5 mg/dl/hr prior to institution of ethanol therapy or dialysis has been reported [2].

Elimination half life of formate has been reported to be 6.04 +/- 3.26 hours. Elimination half life during dialysis has been calculated in 14 patients and was significantly shorter than formate half life without dialysis; 1.80 +/- 0.78 hr, with a dialysis clearance of 176 +/- 43 ml/min [2].

Protein binding: Methanol apparently does not bind to proteins; however, its metabolites formaldehyde and formic acid can react strongly with soluble and insoluble body proteins [2].

Passage of blood-brain barrier: free [3].

Metabolism and excretion
Methanol is slowly metabolized. After ingestion, significant levels of methanol can be found in the body for up to seven days after ingestion. Methanol is initially oxidized to formaldehyde in a reaction catalyzed by alcohol dehydrogenase. The methanol metabolite, formaldehyde, is rapidly oxidized by aldehyde dehydrogenase to formic

acid, which is responsible for the metabolic acidosis and retinal toxicity associated with methanol exposures. There are several mechanisms for the subsequent metabolism of formaldehyde to formic acid:
a. Formaldehyde exists in a hydrated form, methanediol, which is a substrate for alcohol dehydrogenase.
b. A specific formaldehyde dehydrogenase exists in human erythrocytes.
c. Oxidation can occur in liver mitochondria by aldehyde dehydrogenase.
d. Some metabolism may occur through the tetrahydrofolic acid-dependent one-carbon pool [2].

Metabolites more toxic than Methanol: Formaldehye and Formic acid [3].

Excretion: A very small percentage of an ingested dose of methanol (3% to 5%) is excreted unchanged by the kidneys. Approximately 5% of an oral dose of methanol is excreted as formic acid [2].

Toxicological mechanisms
Methanol is converted relatively slowly in the human liver to formaldehyde and then formic acid by the catalytic action of alcohol dehydrogenase and acetaldehyde dehydrogenase. It is these two metabolites of methanol, rather than methanol per se, that are highly toxic and produce the severe metabolic acidosis, ocular symptoms, and other effects of acute methanol poisoning.

Formic acid inhibits cytochrome oxidase activity by binding to the ferric iron moiety; it is less potent in this regard than cyanide and carbon monoxide. The acidosis present in severe methanol poisoning increases the concentration of undissociated formic acid, thus potentiating inhibition of cellular respiration. The result is tissue hypoxia and lactic acid formation, which further add to the undissociated formic acid levels and perpetuates the circle of hypoxic damage. The anion gap observed clinically is due to both lactic acid and formic acid. Secondary to anaerobic glycolysis and lactic acidosis, superoxide anions and hydroxyl radicals are generated, leading to cell membrane damage. There is an influx of calcium into the cell, resulting in mitochondrial dysfunction and cell death.

Target organs: CNS, pancreas, liver, kidney and heart (histopathological organ lesions).

References

1. HSDB, TOXNET (2005).
2. Poisindex, Thomson Micromedex (2005).
3. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall, B., Hallander, S., Walum, E. & Bondesson, I. (1998) MEIC Evaluation of Acute Systemic Toxicity: Part V. Rodent and Human Toxicity Data for the 50 Reference Chemicals, ATLA 26, 571-616.

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