

Elimination Half-life of Methanol During Hangover

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Abstract: This paper reports the elimination half-life of methanol in human volunteers. Experiments were made during the morning after the subjects had consumed 1000-1500 ml red wine (9.5% w/v ethanol, 100 mg/l methanol) the previous evening. The washout of methanol from the body coincided with the onset of hangover. The concentrations of ethanol and methanol in blood were determined indirectly by analysis of end-expired alveolar air. In the morning when blood-ethanol dropped below the K_m of liver alcohol dehydrogenase (ADH) of about 100 mg/l (2.2 mM), the disappearance half-life of ethanol was 21, 22, 18 and 15 min. in 4 test subjects respectively. The corresponding elimination half-lives of methanol were 213, 110, 133 and 142 min. in these same individuals. The experimental design outlined in this paper can be used to obtain useful data on elimination kinetics of methanol in human volunteers without undue ethical limitations. Circumstantial evidence is presented to link methanol or its toxic metabolic products, formaldehyde and formic acid, with the pathogenesis of hangover.

Studies in man on metabolism and kinetics of methanol are hampered by the high toxicity of its metabolites, formaldehyde and formic acid (Røe 1982). Most published work in this field comes from clinical reports about individuals poisoned with methanol (Jacobsen *et al.* 1982). In these situations, however, the elimination kinetics of methanol are confounded because ethanol is almost always administered as a first-aid in treatment (McCoy *et al.* 1979; Peterson 1981). Other therapeutic measures that tend to complicate the pharmacokinetic profile of methanol include haemodialysis to clear the blood from low-molecular species and infusion of bicarbonate to counteract metabolic acidosis (Pappas & Silverman 1982).

Both methanol and ethanol are substrates for hepatic alcohol dehydrogenase (ADH), although the affinity of the enzyme is much higher for ethanol than methanol (Mani *et al.* 1970). This means that biotransformation of methanol can be blocked by administration of ethanol. Moreover, because trace amounts of methanol (<1.0 mg/l) are produced in the body in the course of intermediary metabolism (Eriksen & Kulkarni 1963), the endogenous levels will increase during a period of heavy drinking (Majchrowicz & Mendelson 1971; Magrinat *et al.* 1973). The occurrence of methanol as a congener in various alcoholic beverages adds to this accumulation. It should therefore be possible to investigate the kinetics of methanol elimination without interference from ethanol if experiments are conducted in the morning after a heavy drinking session when blood-ethanol concentrations drop below the K_m of ADH about 100 mg/l (2.2 mM).

This paper reports the elimination half-life of methanol in healthy human volunteers. Experiments were made in the morning after ethanol intoxication the night before and therefore coinciding with onset of hangover. This experimental design allows collecting data on methanol kinetics in human volunteers without having to directly administer methanol and therefore without undue ethical limitations.

Materials and Methods

Subjects and conditions. Four healthy individuals (3 men and 1 woman) all accustomed to moderate drinking volunteered for this study. They arrived at the laboratory at about 8 p.m. and consumed over the following 2 hours between 1000 and 1500 ml red wine (9.5 g/100 ml ethanol; 100 mg/l methanol) together with potato chips and cheese. These doses of ethanol correspond to between 1.2 and 1.5 g ethanol per kg body weight. The peak concentrations of ethanol in blood, calculated from breath analysis, were between 1360-1600 mg/l. The test subjects slept in the laboratory and were woken up at 8.00 a.m. the next morning. The concentration of ethanol remaining in the blood was determined by analysis of expired breath at 15 min. intervals until a level of about 100-200 mg/l was reached. In one experiment, concentrations of endogenous ethanol and methanol were determined the day before and the day after the hangover study to establish basal values. Below a blood concentration of about 100 mg/l, liver ADH is no longer saturated with ethanol as substrate and metabolism of methanol can therefore commence.

In this pilot study, no attempts were made to quantitate the intensity of hangover symptoms or to relate them to the elimination kinetics of methanol. The four test subjects reported that they experienced moderately intense hangover and generally felt tired and thirsty.

Determination of ethanol and methanol. The blood concentrations of ethanol and methanol were estimated indirectly by analysis of breath samples. This technique is well established both in theory and practice (Jones 1983a & 1985a). Samples of end-expired alveolar air were analysed at 15-20 min. intervals from 9.00 a.m.-1.00 p.m. on the morning of hangover. A specially designed gas chromatographic method was used for analysis of breath. This technique has been described in detail elsewhere and involves the use of an on-column gas sampling device (Jones 1985b). In brief, the test subjects took moderately deep inhalations of room air and then exhaled as much breath as possible into one arm of a copper T-tube, maintained at about 50° with heating tapes. The expired breath was lead through a gas-sampling loop positioned inside the oven (130°) of the gas chromatograph. The volume of breath passing through this sampling system was monitored with a Wright Respirometer. An aliquot of breath (2 ml) was captured for analysis when subjects reached vital capacity exhalations. Porapak Q was used as station-

ary phase and methanol and ethanol gave retention times of 1.5 and 3.4 min, respectively.

Calibration of the GC response for ethanol and methanol: The response of the flame ionization detector was calibrated by analysis of known strength air-alcohol standards generated with a breath-simulator device (Dubowski 1979). This entails dynamic equilibration of aqueous standard solutions of ethanol and methanol held at 34 °C. Compressed air was bubbled into these solutions and thereafter passed through the gas sampling loop (2 ml). After circulating the air for about 5–10 sec, a snap sample of the resulting air-alcohol standard vapour was taken for analysis. With this procedure, expired breath from test subjects and calibration standards are sampled and analysed in the same way. From the published values of water:air and blood:air partition coefficients of ethanol (2585 and 2300 respectively) and methanol (3330 and 3231) (Jones 1983a; Jones *et al.* unpublished results), the GC response can be calibrated and blood-alcohol concentrations calculated indirectly from breath analysis.

Results

Fig. 1 shows the washout curves of ethanol and methanol in one individual subject in the morning after a heavy drinking session the night before. Note that at the low concentrations of ethanol (< 100 mg/l) the elimination time course follows first-order kinetics with a half-life of 15 min. The half-life of methanol however was almost 10 times longer (142 min.). This fits with results from *in vitro* experiments on kinetic properties of human ADH and its relative affinity for different substrates (Mani *et al.* 1970).

Elevated concentration of methanol will therefore persist in the blood for about 10 hrs after ethanol has reached endogenous levels ($5 \times t_{1/2}$). An abnormally high concentration of methanol in blood or breath can serve as a biochemical marker of recent heavy drinking (Jones 1986). The half-lives of ethanol elimination in the other volunteer subjects at low substrate concentrations (below the K_m of ADH) were 21, 22 and 18 min, respectively and the corresponding half-lives of methanol were 213, 110 and 133 min.

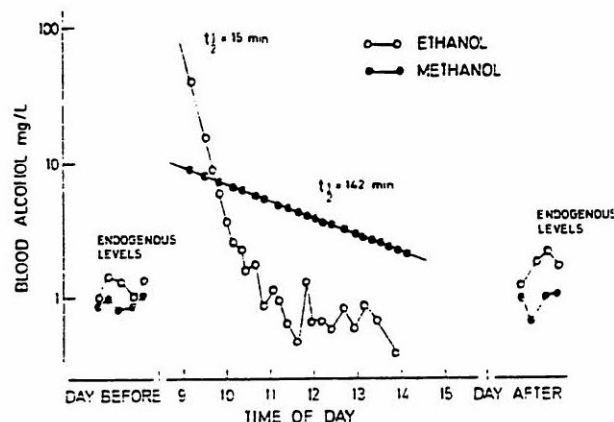


Fig. 1. Concentration-time profiles of ethanol and methanol elimination in one male subject during the morning of hangover. The concentrations of endogenous ethanol and methanol are also shown in tests made the day before and after the hangover study. Blood concentrations of these alcohols were estimated indirectly by analysis of end-expired breath. $t_{1/2}$ = elimination half-life.

Discussion

Leaf & Zatzman (1952) studied absorption, distribution and elimination of methanol and administered small doses of methanol (2.5–7.0 ml) to human subjects. From analysis of methanol in urine samples, they showed first order elimination kinetics. I have calculated from their data that the urinary elimination half-life was 179 ± 8 min. (mean \pm S.D.) based on experiments at 3 doses of methanol in each of 3 male subjects. This figure agrees fairly well with half-lives reported in the present experiments, 142, 213, 110 and 133 min. Furthermore, Jacobsen *et al.* (1982) reported that during haemodialysis in two patients poisoned with methanol, the elimination half-lives were 219 and 197 min.

Majchrowicz & Mendelson (1971) showed that when alcoholics consumed alcohol over a period of several days or weeks reaching blood-ethanol concentrations of 1500–4500 mg/l the methanol levels in blood and urine progressively increased to 20–40 mg/l. These workers noted that the elimination of methanol lagged behind ethanol by 12–24 hours and followed approximately the same time course as ethanol withdrawal symptoms. Majchrowicz (1975) speculated on the role of methanol and/or its metabolites in alcohol withdrawal and hangover. My work confirms and extends these findings by showing a rise in blood-methanol in healthy individuals even after a single evening's drinking. This observation has been used to measure the elimination half-life of methanol in human volunteers. To establish whether the metabolites of methanol are associated with metabolic acidosis, previously reported during hangover, one needs to demonstrate an elevated concentration of formate ions in the blood. Otherwise it will be impossible to differentiate formic-acid induced metabolic acidosis from the disturbed acid-base balance caused by abnormal concentrations of lactic acid, ketone bodies and free fatty acids in blood during hangover (Ylikahri *et al.* 1974b).

The mechanism whereby acute ethanol intoxication causes hangover remains an unsolved problem in biological alcohol research. Comprehensive studies with main focus on metabolic disturbances during hangover were reported by Ylikahri *et al.* (1974a, 1974b & 1976). These workers failed to find any clearcut associations between peak blood concentrations of ethanol or acetaldehyde after drinking and intensity of hangover (Ylikahri *et al.* 1974a). The most consistent metabolic changes during hangover were disturbed acid-base balance, lowered blood pH and acidosis (Ylikahri *et al.* 1974b). A later study, however, demonstrated that the metabolic acidosis could be counteracted by administration of fructose or glucose together with ethanol and in the morning during hangover. This treatment with sugar failed to alleviate the unpleasant symptoms of hangover (Ylikahri *et al.* 1976).

It is generally known that consumption of alcoholic beverages rich in congeners (including methanol) causes more severe hangover than equivalent doses of pure ethanol or vodka (Chapman 1970; Pawan 1972). On the other hand, many individuals deny suffering from hangover despite

and drinking (Smith & Barnes 1983). The most effective treatment for hangover, at least for short periods, is to drink more ethanol. The resulting increase in blood-ethanol may serve to block the conversion of methanol into formaldehyde and formic acid. Formic acid has a pKa of 3.75 and acidosis is a common finding during ethanol withdrawal in alcoholics and problem drinkers (Miller *et al.* 1978; Magrinat *et al.* 1973).

Human ADH occurs in multiple molecular forms and the isoenzyme pattern of a particular individual seems to be genetically determined (Vallee & Bazzone 1983; Von Wartburg & Bühler 1984). Moreover, the kinetic properties of ADH isoenzymes differ widely in terms of activity coefficient, Km value, and relative specificity for different substrates. Some individuals might be equipped with ADH isoenzymes that possess high affinity for methanol as substrate leading to a more effective production of formaldehyde and formic acid during hangover. The first metabolite of methanol, formaldehyde, is a reactive chemical substance. Under physiological conditions it easily condenses with biogenic amines as well as other endogenous species and can possibly yield pharmacologically active products. Moreover, formaldehyde can bind to proteins in a way that might alter the structure of cell membranes and thereby change the conformation of receptors (Heck & Casanova-Schmitz 1985). The lethal dose of methanol in humans shows pronounced individual differences ranging from 15 ml to 500 ml (Bennett *et al.* 1953; Pappas & Silverman 1982). This indicates distinct interindividual differences in sensitivity to methanol's toxic metabolites and could reflect different rates of enzymatic breakdown.

Considerable circumstantial evidence can be mustered to link biotransformation of methanol with the onset of hangover. If this could be confirmed experimentally then, instead of treating hangover with ethanol the orphan drug 4-methyl pyrazole (4-MP), a potent inhibitor of ADH isoenzymes, might prove effective. This approach will be more acceptable for clinical purposes than administration of more ethanol which acts to prolong the hangover or detoxification process. The use of 4-MP has already been recommended as replacement for ethanol in treatment of methanol poisoning (Blomstrand *et al.* 1979).

My hypothesis linking methanol oxidation and hangover can be tested experimentally if 5–10 g of pure methanol is given to hangover-prone individuals. This dose will result in peak blood concentrations between 100–200 mg/l (3.1–6.2 mM) if methanol, like ethanol, has a distribution volume of 0.7 l/kg. If hangover develops during washout of this non-intoxicating blood-alcohol concentration then this would strongly incriminate the oxidation products of methanol either directly or indirectly as a cause of hangover. However, a university ethical committee will find it difficult to approve this study. In the work reported by Leaf & Zatman (1952) the occurrence of unpleasant hangover symptoms was unfortunately not recorded. Indeed, the volunteers may have been among those that normally do not experience hangover.

If metabolites of methanol play a role in hangover and if hangover symptoms can be alleviated by taking 4-methyl pyrazole then pharmaceutical companies might be willing to set-up the necessary experimental protocol to test this notion. The orphan drug 4-methyl pyrazole might eventually become adopted. Hangover is a major social-medical problem throughout the Western World with significant costs to the individual and society in terms of industrial accidents and lost working hours.

Acknowledgments

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