Royal College of Physicians of Ireland

RCPI Policy Group on Alcohol

Reducing Alcohol Health Harm

Supplementary Information:

Biochemical Considerations with Alcohol

Biochemical considerations with alcohol

1. Summary

Over 90% of alcohol consumed is oxidized in the liver. Most of the remainder is excreted through the lungs and in the urine. Ethanol is 95% metabolised in the liver. 5% is eliminated through all secretions, urine and by evaporation. At higher concentrations ethanol elimination is zero order kinetics independent of the dose. At low levels less than 20 mg/dl, the kinetics are non-linear and are first order. First order also applies at very high levels[1]. Women show a 13 – 22% faster rate of ethanol elimination than men and a 9 to 14% smaller volume of distribution.

Rate of elimination

There are many estimates of the rate of elimination of ethanol from blood. A rate derived from drinking drivers was 19.1 ± 4.9 mg/dl/h (mean ± SD) with the 95% confidence limits 9 to 29 mg/dl/h[2]. At very high blood levels in the range 271 – 518 mg/dl, the average rate of ethanol elimination was 33 mg/dl/h with the range of 20 to 62 mg/dl/h[3].

This ultra-rapid elimination of ethanol in some cases makes calculations in legal cases approximate. The degree of uncertainty in the conventional calculations of the number of drinks taken and the level of blood ethanol back-calculated to an event hours earlier is much greater than often appreciated. Induction of the microsomal CYP2E1 pathway for ethanol oxidation by chronic high level alcohol consumption is probably the mechanism. In the ethanol elimination phase, the urine/blood ratio is about 1.3 but there are wide variations in the literature[4].

Metabolic changes in alcoholism.

These include hyperuricaemia, lactic acidosis, hypertriglyceridaemia, hypoglycaemia, hyperglycaemia, hypophosphataemia and hypomagnesaemia. Starving alcoholics may have ketoacidosis which may be dangerous[5]. Alcoholic liver disease often is accompanied by raised body iron stores as shown by increased transferring saturation and serum ferritin[6].

2. Toxicology and Alcohol

Clinical effects of toxic alcohol levels

Blood ethanol between 350 to 450 mg/dl may cause hypothermia, hypotension, stupor, coma, depressed reflexes, hypoglycaemia, convulsions, respiratory depression, metabolic acidosis and cardiac arrhythmias. At levels of 450 mg/dl, deep coma, respiratory depression or arrest and circulatory failure may occur. Individual susceptibility to the effects of alcohol is wide.

Ethanol related deaths

The National Drug-Related Deaths Index (NDRDI) has published the Irish national data for ethanol related deaths and deaths among people who were alcohol dependent over the period 2004 to 2008[7]. There were 672 poisoning deaths where ethanol played a role over the five years. In that period, fatal ethanol only poisonings occurred in 331 people; median age 48 year and 66.8% were male with fatal polysubstance poisonings totalling another 341 cases. The median age of death was 59 years and 65.2% were aged 64 years or under. Over 36.8% of the deaths in the 25 – 34 year age group were due to alcoholic liver disease. When trauma was the proximate cause of death, 39.9% were due to falls and 19.4% due to hanging.

Lethal alcohol levels

Various concentrations are quoted for ranges of lethal blood ethanol values. These are 350-400 mg/dl[8], 400 mg/dl[9], 225 to 400 mg/dl[10]and >350 mg/dl[11]. In a review of 693 fatal acute ethanol poisonings, the median blood ethanol concentrations was 360 mg/dl and the 5th and 95th percentiles were 220 mg/dl and 500 mg/dl respectively. These data are considered an underestimate of the peak ethanol involved as metabolism will continue up to the time of death. Data in 825 people with chronic alcoholism were a median blood ethanol of 150 mg/dl at the time of autopsy with 5th and 95th percentiles of 14 to 410 mg/dl[12]. Vitreous samples at post-mortem are the most likely to be stable and may help to differentiate post-mortem endogenous alcohol production from those levels present at the time of death.

3. Alcohol Metabolism

Two major pathways of alcohol metabolism to acetaldehyde have been identified. Acetaldehyde is then oxidized by a third metabolic process.

Alcohol dehydrogenase and aldehyde dehydrogenase (ALDH) are inhibited by fomepizole (used to treat ethylene glycol poisoning) and disulfiram (antabuse in alcoholism), respectively. The primary pathway for alcohol metabolism involves ADH, a cytosolic enzyme that catalyzes the conversion of alcohol to acetaldehyde. This enzyme is located mainly in the liver, but it is also found in the brain and stomach. During conversion of ethanol to acetaldehyde, a hydrogen ion is transferred from alcohol to the cofactor nicotinamide adenine dinucleotide (NAD+) to form NADH. As a net result, alcohol oxidation generates an excess of reducing equivalents in the liver, chiefly as NADH.

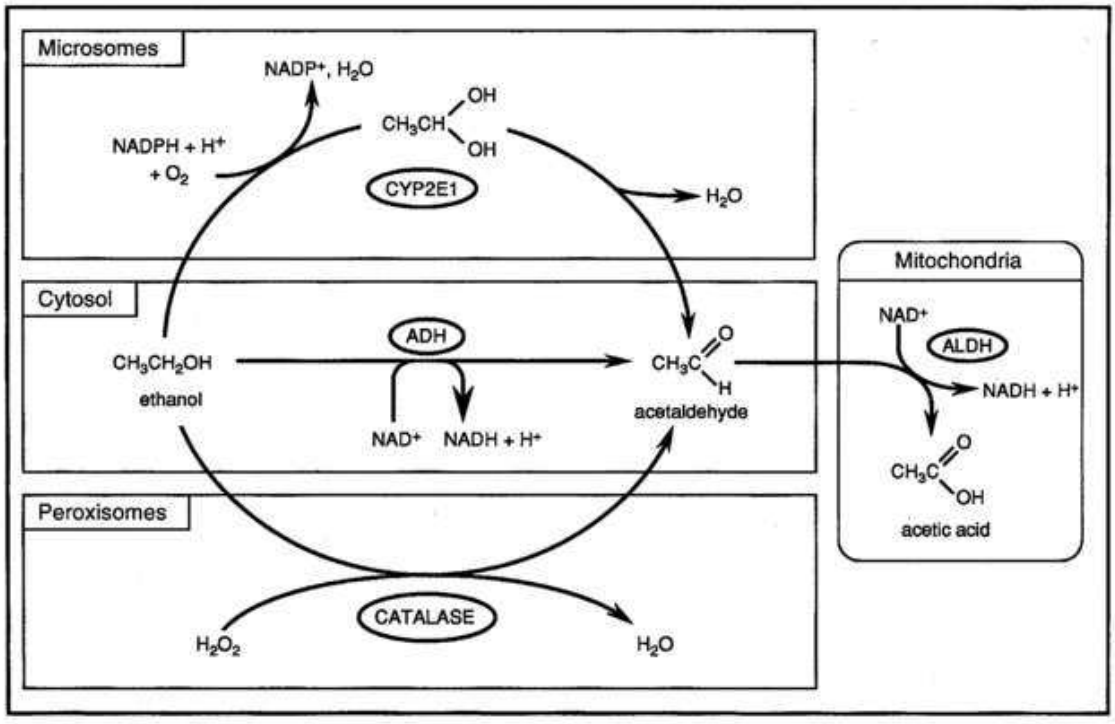


Figure 1: Metabolism of ethanol by alcohol dehydrogenase (ADH) and the microsomal ethanol-oxidizing system (MEOS) . CYP2E1 is cytochrome P450 2E1. There is also a small amount of alcohol metabolised in the brain to acetaldehyde by catalase.

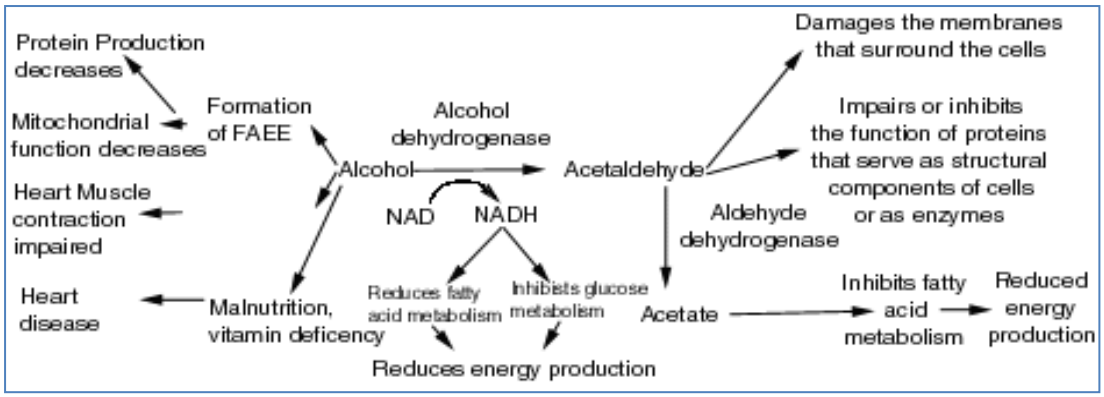
The Microsomal Ethanol Oxidizing System (MEOS) uses NADPH as a cofactor in the metabolism of ethanol. At blood concentrations below100 mg/dL (22 mmol/L), the MEOS system, which has a relatively high Km for alcohol, contributes little to the metabolism of ethanol. However, when large amounts of ethanol are consumed, the alcohol dehydrogenase system becomes saturated owing to depletion of the

required cofactor, NAD+. As the concentration of ethanol increases above 100 mg/dL, there is increased contribution from the MEOS system, which does not rely upon NAD+ as a cofactor. The MEOS system contributes < 10% of alcohol metabolism. During chronic alcohol consumption, MEOS activity increases. As a result, chronic alcohol consumption results in significant increases not only in ethanol metabolism but also in the clearance of other drugs eliminated by the MEOS system.

Aldehyde

Much of the acetaldehyde formed from alcohol appears to be oxidized in the liver in a reaction catalyzed by mitochondrial NAD-dependent aldehyde dehydrogenase to acetate. Acetate is conjugated to coenzyme A and the resulting Acetyl-CoA can be metabolised in the Krebs cycle to CO_2 and water or utilised for the synthesis of fatty acids which leads towards fatty liver.

The wide ranging metabolic effects of alcohol and its degradation products acetaldehyde and acetate are summarised schematically below[13]. Fatty acid ethyl esters (FAEE) are potentially toxic derivatives of fatty acids. Nicotinamide adenine dinucleotide (NAD) is a coenzyme that plays an accessory role in enzyme catalysis. NADH is the reduced form of NAD.



Acetaldehyde is probably the primary toxin causing liver damage as well as stimulating fibrosis leading to cirrhosis. The injury is caused by oxidative stress caused by reactive species formed by alcohol induction of CYO 2E1[14].

Asians have a variant of ADH (ADH1B*2 or ADH1C*1) which speeds the metabolism of alcohol to acetaldehyde and about 50% have a variant of ALDH which slows the metabolism of acetaldehyde. This makes drinking alcohol less enjoyable but more toxic for Asians with the consequence of reduced rates of alcohol dependence[15].

Facial flushing is indicative ALDH2 deficiency and drinkers with that condition have a much increased risk of oesophageal carcinoma.

Laboratory markers of alcohol use and abuse[16]

- Blood, Breath and Urine Alcohol (ethanol) – These will only be raised acutely with alcohol consumption.
- Serum γ-glutamyl transferase (GGT) are elevated in about 75% who are alcohol-dependent with a range of sensitivities of 60-90% and specificity of 55-100%. The half-life is about 14 to 26 days and it usually returns to normal values 4-5 weeks after alcohol cessation. Usually 50-72% of raised GGT levels are due to excess alcohol consumption.
- Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually raised 2-4 times the upper limit of normal in alcoholics. The sensitivities are 25-60% for AST and 15-40% for ALT. An AST/ALT ratio >2 almost indicates alcohol-induced liver damage. The ratio is a simple and good simple separator of alcohol induced and non-alcohol induced liver disease[17]. The serum aminotransferases rarely exceed 300 U/L in acute alcoholism because alcohol depletes vitamin B_6-dependent pyridoxal-5-phosphate which is an essential precursor of aminotransferase synthesis.
- Mean corpuscular volume (MCV) is raised in chronic high intake alcohol consumption greater than 60 g alcohol daily. It has low sensitivity of 40-50% but specificity of 80-90%. Few non-drinkers will have raised MVC values.
- High density lipoprotein and triglycerides are likely to be raised with heavy drinking.
- Serum IgA is usually raised in alcohol-induced liver disease as are urinary coproporphyrins.
- Serum urate is raised in about 20-40% of alcoholics.
- Serum carbohydrate-deficient transferrin has a sensitivity of 82% and a specificity of 97% in established alcoholics[18]. It is more sensitive than GGT in detecting relapses during treatment and it is better at distinguishing alcoholic from non-alcoholic liver disease.
- Serum mitochondrial AST (mAST) has a sensitivity of about 90% in alcoholic patients but the specificity is low. Cytosolic AST makes up >90% of normal AST

in healthy individuals. mAST may have a role in a specialist unit in distinguishing alcohol and non-alcohol induced liver disease.

- Serum and urine 5-hydroxytryptophol (5-HTOL). 5-HTOL with 5-hydroxy-tryptophol-3-acetic acid (5-HIAA) are metabolites of serotonin. Alcohol shifts the metabolism of serotonin towards 5-HTOL in a dose dependent manner. The 5-HTOL: 5-HIAA ratio reflects alcohol intake in the past 24h and remains elevated for 6-15 h after the blood alcohol has cleared[19]. Chromatographic methods make their use inconvenient.
- Serum ß-hexosaminidase (ß-HEX) is an acid lysosomal glycoside. It is a sensitive 70-90% in detecting heavy drinking and is more sensitive than GGT. The ß-HEX isoform is highly indicative of alcohol abuse[20]. But elevated levels are also found in other common conditions including cerebral and myocardial infarction, hypertension, diabetes mellitus, cirrhosis and pregnancy.
- Haemoglobin-acetaldehyde adduct correlates with the volume of alcohol intake and in a rehabilitation unit, the sensitivity was 67% and specificity 77% which is better than GGT, AST or MCV[21].
- Other potential markers of alcohol excess include fatty acid ethyl esters, phosphatidylethanol, sialic acid, ethythrocyte aldehyde dehydrogenase, plasma α-aminobutyric acid/leucine ratio, urinary salsolinol and urinary dolichols. None of these offer clinical advantages over more conventional biochemical markers[16].
- Ethyl glucuronide and ethyl sulphate are direct metabolites of ethanol. Their presence in urine indicates that ethanol was ingested within the previous 3 or 4 days. But the published elimination data show a wide variation. A study in alcohol-dependent patients revealed individual values returning to below the cut-off limit of <500 ng/ml in 40 to 130 hours with a median of 78 hours[22].
- Combinations of CDT plus GGT or CDT plus MCV enhance sensitivity but are not used in practice.

References

[1] Bogusz M, Pach J, Stasko W. Comparative studies on the rate of ethanol elimination in acute poisoning and in controlled conditions. J Forensic Sci 1977;22:446-51.

[2] Jones AW, Andersson L. Influence of age, gender, and blood-alcohol concentration on the disappearance rate of alcohol from blood in drinking drivers. J Forensic Sci 1996;41:922-6.

[3] Jones AW. Ultra-rapid rate of ethanol elimination from blood in drunken drivers with extremely high blood-alcohol concentrations. Int J Legal Med 2008;122:129-34.

[4] Heise HA, Concentrations of alcohol in samples of blood and urine taken at the same time. J Forensic Sci 1967;12:454-62.

[5] Brinkmann B, Fechner G, Karger B, DuChesne A. Ketoacidosis and lactic acidosis – frequent causes of death in chronic alcoholics. Int J Leg Med 1989;111:115-9.

[6] Harrison-Findik DD. Role of alcohol in the regulation of iron metabolism. World J Gastroenterol 2007;13:4925-30.

[7] Lyons S, Lynn E, Walsh S, Sutton M, Long J. Alcohol-related deaths and deaths among people who were alcohol dependent in Ireland, 2004 to 2008. HRB Trends Series 10. Dublin: Health Research Board. http://www.hrb.ie/uploads/tx_hrbpublications/HRB_Trend_Series_01.pdf (accessed 17th September 2012)

[8] Schulz M, Schmolot A. Therapeutic and toxic blood concentrations of more than 500 DRUGS. Pharmazie 1997;52:895-91.

[9] Repetto MR , Repetto M. Concentrations in human fluids: 101 drugs affecting the digestive system and metabolism. J Toxicol Clin Toxicol 1999;37:1-8.

[10] Stead AH, Moffat AC. A collection of therapeutic, toxic and fatal blood drug concentrations in man. Human Tox 1983;3:437-64.

[11] Winek CL, Wahba WW, Winek Jr CL, Winek-Balzer TW. Drug and chemical blood-level data 2001. Forensic Sci Int 2001;122:107-23.

[12] Jones AW, Holmgren P. Comparison of blood-ethanol concentration in deaths attributed to acute alcohol poisoning and chronic alcoholism. J Forensic Sci 2003;48:1-6.

[13] Alcohol metabolism. Institute for Circumpolar Health Studies. University of Alaska Anchorage. http://www.uaa.alaska.edu/instituteforcircumpolarhealthstudies/caas/research/alc_met.cfm Accessed 15 September 2012

[14] Tsukamoto H, Rippe R, Niemela O, Lin M. Roles of oxidative stress in activation of Kupffer and Ito cells in liver fibrinogenesis. J Gastroenterol Hepatol 1995;10:550 -553.

[15] Eng MY, Luczak SE, Wall TL. ALDH2, ADH1B, and ADH1C genotypes in Asians: a literature review. Alcohol Res Health 2007;30:22-7.

[16] Sharpe PC. Biochemical detection and monitoring of alcohol abuse and abstinence. Ann Clin Biochem 2001;38:652-664.

[17] Sharpe PC, McBride R, Archbold GPR. Biochemical markers of alcohol abuse. Q J Med 1996:89:137-44.

[18] Stibler H Carbohydrate-deficient transferring in serum: a new marker of potentially harmful alcohol consumption reviewed. Clin Chem 1991;37:2029-37.

[19] Helander A, Beck O, James AW. Laboratory testing for recent alcohol consumption: comparison of ethanol, methanol and 5-hydroxtryptophol. Clin Chem 1996;42:618-24.

[20] Hultberg B, Isaksson A, Berglund M, Alling C. Increase and time-course variations in ß-hexoseaminidase isoenzyme B and carbohydrate deficient transferring in serum from alcoholics and similar. Alcohol Clin Exp Res 1995;19:452-6.

[21] Hazelett SE, Liebelt RA, Brown WJ, Androulakakis V, Jarjoura D, Truitt EBjr. Evaluation of acetaldehyde-modified haemoglobin, carbohydrate deficient transferring (CDT) and haemoglobin abnormalities in chronic alcoholism. Alcohol Clin Exp Res 1998;22:1813-9.

[22] Helander A, Böttcher M, Fehr C, Dahmen N, Beck O. Detection times for urinary ethyl glucuronide and ethyl sulphate in heavy drinkers during alcohol detoxification. Alcohol and alcoholism 2009;44:55-61.