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Review

Evidence-based survey of the elimination rates of ethanol from blood with applications in forensic casework

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ABSTRACT

Reliable information about the elimination rate of alcohol (ethanol) from blood is often needed in forensic science and legal medicine when alcohol-related crimes, such as drunken driving or drug-related sexual assault are investigated. A blood sample for forensic analysis might not be taken until several hours after an offence was committed. The courts usually want to know the suspect's blood-alcohol concentration (BAC) at some earlier time, such as the time of driving. Making these back calculations or retrograde extrapolations of BAC in criminal cases has many proponents and critics. Ethanol is eliminated from the body mainly by oxidative metabolism in the liver by Class I isoenzymes of alcohol dehydrogenase (ADH). Ethanol is an example of a drug for which the Michaelis–Menten pharmacokinetic model applies and the Michaelis constant (k_m) for Class I ADH is at a BAC of 2–10 mg/100 mL. This means that the enzyme is saturated with substrate after the first few drinks and that zero-order kinetics is adequate to describe the declining phase of the BAC profile in most forensic situations (BAC > 20 mg/100 mL). After drinking on an empty stomach, the elimination rate of ethanol from blood falls within the range 10–15 mg/100 mL/h. In non-fasted subjects the rate of elimination tends to be in the range 15–20 mg/100 mL/h. In alcoholics during detoxification, because activity of microsomal enzyme (CYP2E1) is boosted, the ethanol elimination rate might be 25–35 mg/100 mL/h. The slope of the BAC declining phase is slightly steeper in women compared with men, which seems to be related to gender differences in liver weight in relation to lean body mass. The present evidence-based review suggests that the physiological range of ethanol elimination rates from blood is from 10 to 35 mg/100 mL/h. In moderate drinkers 15 mg/100 mL/h remains a good average value for the population, whereas in apprehended drivers 19 mg/100 mL/h is more appropriate, since many of these individuals are binge drinkers or alcoholics. In preparing this article, a large number of peer-reviewed publications were scrutinized. Only those meeting certain standards in experimental design, dose of alcohol and blood-sampling protocol were used. The results presented can hopefully serve as best-practice guidelines when questions arise in criminal and civil litigation about the elimination rate of ethanol from blood in humans.

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1. Introduction

Knowledge about absorption, distribution, metabolism and elimination (ADME) of ethanol is important in forensic science and legal medicine whenever alcohol-related crimes are investigated [1,2]. Binge drinking and drunkenness are over-represented in many crimes of violence, which makes the analysis and interpretation of a person's blood-alcohol concentration (BAC) an important task for forensic science and toxicology laboratories [3].

Questions about the disposition and fate of ethanol in the body are important during the prosecution of alcohol-impaired drivers because there is often a requirement to perform a back-calculation. This entails calculating a suspect's BAC at the time of driving from the BAC determined at the time of sampling blood, which is often a few hours later [4–7]. During prosecution in alleged sexual assault cases, blood and urine specimens for toxicological analysis are usually obtained several hours after the incident [8]. The courts want to know the victim's BAC at the time of the attack so that an opinion can be reached about incapacitation and the ability to consent to sexual activity [9,10]. Another example from criminal prosecution is intoxicated automatism when an opinion is needed about a person's behaviour in relation to alcohol or drug influence and whether a crime was committed without conscious knowledge [11].

Physiological research on the disposition and fate of alcohol in the body began in the 1920s with the seminal works of Erik MP Widmark (1889–1945). His monograph from 1932, which was originally written in German and translated and re-published in English 50 years later, remains essential reading today [12–14]. In this monograph, the fundamental principles of ADME of ethanol were established and a method was described to evaluate concentration–time profiles of ethanol in quantitative terms including the rate of elimination from blood (β) and the volume of distribution (V_d) or in Widmark's terminology the rho factor.

2. Alcohol in the body

The bulk of the dose of alcohol ingested (90–98%) is metabolized primarily in the liver and the remaining 2–10% is excreted unchanged in breath, sweat and urine [15–17]. Two main hepatic enzymes are responsible for oxidative metabolism of ethanol. The first and most important enzyme is alcohol dehydrogenase (ADH) Class I, which is located in the cytosol or soluble fraction of the hepatocytes [18,19]. The second is a membrane-bound enzyme (CYP2E1), located in the smooth endoplasmic reticulum of the microsomes [20–22]. Class I ADH has a low k_m (Michaelis constant of about 2–10 mg/100 mL) with ethanol as substrate so the enzyme becomes saturated after the first couple of drinks [23]. By contrast, the k_m of CYP2E1 is higher (60–80 mg/100 mL), which makes this enzyme more important in clearing ethanol from the blood after heavy drinking, when the BAC exceeds 100 mg/100 mL, which it often does in drunken drivers and other forensic science situations [22,24,25].

Another important enzyme involved in the biotransformation of ethanol is low k_m aldehyde dehydrogenase (ALDH), which is located in the mitochondria of liver cells and its main function is to convert the toxic metabolite acetaldehyde into benign acetate [18,26–28]. The acetate produced during metabolism of ethanol undergoes extra-hepatic metabolism into Acetyl-CoA, which enters the Krebs cycle and is eventually converted into the end products CO_2 and H_2O [23,29].

Enzymatic activity depends on a combination of genetic and environmental factors [30]. Two variants of the Class I ADH enzyme (ADH2B and ADH2C) are functionally polymorphic. ADH2B produces three active peptides (ADH2B1, ADH2B2 and ADH2B3) previously denoted β_1, β_2 and β_3 [31–33]. The corresponding ADH2C gene forms two active peptides (ADH2C1 and ADH2C2) known earlier as γ_1 and γ_2 and these too are involved to a varying extent in the metabolism of ethanol. The individual ADH subunits combine in various ways to give protein products with different catalytic activity, including k_m and V_{max} and this difference probably accounts for variations in rates of ethanol metabolism between different individuals [34,35].

Inter-individual variations in CYP2E1 activity seems to depend more on environmental factors, such as obesity, fasting, previous exposure to alcohol and use of certain prescription drugs [22,25]. Another feature of the CYP2E1 enzyme is its ability to oxidize ethanol faster after chronic exposure to substrate, such as after a period of continuous heavy drinking [36,37]. The extent and duration of exposure to alcohol necessary to cause enzyme induction is not well established and some alcoholics, despite a period of heavy drinking, have elimination rates from blood comparable with occasional drinkers [38]. Nevertheless, the faster rates of ethanol elimination often observed in alcoholics during detoxification (see later) are generally accounted for by the induction of CYP2E1 enzyme [39].

Ethanol is a good example of a drug that exhibits dose-dependent or saturation kinetics, because the principal metabolizing enzyme (hepatic Class I ADH) is saturated at low BAC [40–42]. The typical BAC encountered in forensic science casework ranges from 50 to 500 mg/100 mL, which means that for all practical purposes the elimination of ethanol from blood is adequately described by assuming zero-order kinetics [43]. During the post-absorptive phase, the BAC decreases at a constant rate per unit time until the concentration drops to 20 mg/100 mL, after which the elimination tends to follow first-order kinetics [44,45]. Most therapeutic drugs, unlike ethanol, are eliminated from blood by first-order kinetics, the rate being proportional to the prevailing drug concentration [46,47].

Fig. 1 illustrates the fate of alcohol in the body showing oxidative and non-oxidative pathways of metabolism and the

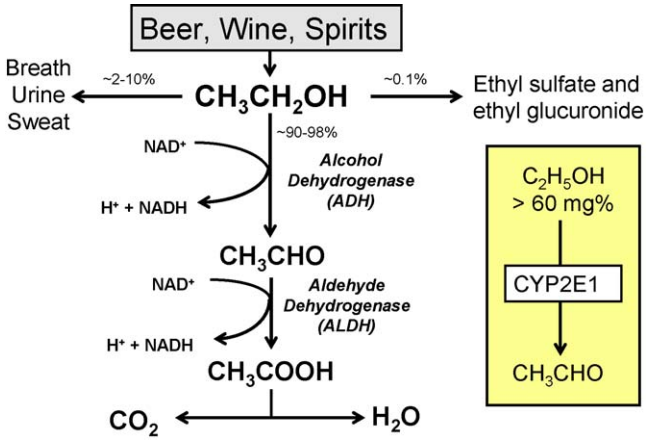

Fig. 1. Human metabolism of ethanol illustrating oxidative and non-oxidative pathways and the relative amounts excreted unchanged. The CYP2E1 enzyme has a higher k_m for ethanol as substrate compared with ADH and becomes more important in metabolism when blood-alcohol concentration exceeds 60 mg/100 mL.