The Pharmacokinetics of Alcohol in Healthy Adults

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The Pharmacokinetics of Alcohol in Healthy Adults

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Abstract

Alcohol is a commonly used drug that has many important health consequences. To understand its physiological effects and predict drug interactions it is important to understand alcohol's pharmacokinetics and the factors that influence it. A brief review of the absorption, distribution, metabolism, and excretion of alcohol is provided. Along with a discussion of important factors that influence these stages of alcohol pharmacokinetics.

Introduction

Alcohol (ethanol) is the most widely used drug worldwide [1, 2]. Moderate intake is associated with health benefits but excessive intake is detrimental to health and the society. Current British guidelines for the consumption of alcohol reflect this by discouraging chronic excess and binge drinking and recommending that males do not regularly drink more than 3-4 units and females not more than 2-3 units of alcohol per day [3]. Alcohol misuse is associated with significant morbidity and mortality and alcohol related harm is estimated to cost the NHS in England £2.7 billion per year [4]. Alcohol intake can lead to pleasurable effects such as inhibition, and euphoria, as well as sedation and mild anaesthesia at higher concentrations [5]. However, blood alcohol concentrations (BAC) as low as 30 mg/100mL are associated with an increased risk of accidental injury [5]. BAC of 160-200 mg/100mL cause ataxia, dysarthria and loss of consciousness and levels over 400 mg/100mL are usually fatal. The prevalence of alcohol use and the problems it can cause necessitates that health care providers understand alcohol’s pharmacokinetics to provide greater insight into its physiological and pathological effects and any likely drug interactions. Alcohol pharmacokinetics also has important medico-legal implications, for example in cases concerning drink drive charges [6, 7]. These issues have led to the pharmacokinetics of alcohol being widely studied [7-9]. The aim of this article is to provide a brief overview of the factors affecting alcohol pharmacokinetics to aid understanding of the physiological influences of alcohol in healthy adults.

Review

Absorption and distribution

The alcohol molecule is a small polar molecule with both lipophilic and hydrophilic characteristics [1]. The amphipathic qualities of alcohol help to explain its pharmacokinetics within the body. The lipophilic qualities explain how alcohol is absorbed by passive diffusion across the cell membranes without the need for modification. The hydrophilic combined with the polar properties of the alcohol molecule explain how alcohol is completely soluble in water and thus has a similar volume of distribution to total body water (TBW).

Blood alcohol concentration (BAC) is determined by the various factors (table 1) that affect the rate at which alcohol is absorbed, distributed, metabolised and excreted from the body [10]. Following oral administration absorption and distribution determines the proportion and rate at which orally ingested alcohol reaches the blood and body tissues (bioavailability). As alcohol is a small water soluble molecule that can cross cell membranes, it is absorbed from both the stomach (20 %) and the upper small intestine (80 %) [5, 6]. The rate of absorption varies significantly in both intraindividual and interindividual comparisons even after standardised conditions [11]. This suggests that intraindividual variability is due to variation in gastrointestinal function (gastric emptying, intestinal transit time, and portal blood flow). The rate of gastric emptying has a significant impact on the speed at which alcohol is absorbed, because alcohol is absorbed much faster from the small intestine, than it is from the stomach [11]. Factors which affect alcohol availability and gastric emptying (table 2) will greatly influence the rate of absorption. For example, the consumption of alcohol with food inhibits absorption because approximately 20% of the ingested alcohol is oxidised before it can be absorbed [5, 6]. The speed of absorption is also influenced by variation in portal blood flow, because alcohol crosses the biological membrane by passive diffusion [1, 5] thus good blood flow will maintain the concentration gradient and promote absorption. Any stimulation of the sympathetic nervous system (e.g. emotional state or exercise) will reduce portal blood flow and gastric motility thus decreasing alcohol absorption. The type of drink consumed also plays a role. Drinks with...
alcohol content between 20-30% are absorbed quickest [5]. Whereas drinks with a higher alcohol content are absorbed more slowly, because an alcohol content over 30% irritates the gastric mucosa increasing mucus secretion and decreasing gastric emptying. Thus drinks with an alcohol content above 30% can cause a faster rise in BAC if served diluted with a mixer, than if they are served without dilution. This is especially true if the mixer is a carbonated drink as this can also increase the rate of absorption [5].

The bioavailability of alcohol is reduced by first pass metabolism (FPM). Oxidation of alcohol by gastric alcohol dehydrogenase (ADH) in the gastric mucosa accounts for a small proportion of FPM, but the majority occurs via oxidation by ADH in the liver hepatocytes [1, 2, 5, 11]. The proportion of alcohol that is absorbed, and escapes FPM enters the systemic circulation and is rapidly distributed throughout the body tissues via the blood plasma until an equilibrium between the BAC and tissue concentration is reached [1, 6]. The time until equilibrium is dependant upon the permeability (water content), rate of blood flow and mass of the tissue [10], but is generally achieved within 1-2 hours [1, 6]. The same amount of alcohol absorbed can affect different people in different ways [5]. Differences in TBW will influence alcohol pharmacokinetics because it determines the volume of distribution available for alcohol distribution within the body. Alcohol is preferentially distributed in tissues with higher water contents and a good blood supply (e.g. brain and skeletal muscle). Body composition is therefore an important consideration in pharmacokinetic studies [12] because both body size and composition will have a significant impact on the volume of distribution. Females generally have a proportionately smaller lean body mass and a smaller blood volume [5, 10]. The result is a lower volume of distribution and higher BAC when females ingest the same amount of alcohol as men [10]. It has also been suggested that higher BAC may be due to lower FPM by gastric ADH in the gastric mucosa of females [8]. This would increase the bioavailability of alcohol resulting in increased BAC. However, the ability of gastric ADH to metabolise significant amounts of alcohol has been questioned because its activity is 100 times lower then hepatic ADH [11] and more recent studies have failed to support this finding [13, 14].

Metabolism and Excretion

The metabolism and elimination parameters of alcohol are more consistent than the absorption and distribution [9]. A small proportion (2-5%) of the alcohol absorbed is excreted unchanged in the urine, sweat or breath [5, 2] but the majority (~ 90%) is removed via oxidation by ADH [10, 2]. This can occur in various organs such as the stomach and small intestine but is primarily carried out by hepatic ADH [15]. Oxidation by ADH converts alcohol to acetaldehyde, a reactive and toxic molecule that is rapidly oxidised by aldehyde dehydrogenase to harmless acetate. Under normal conditions acetate is then oxidised in the liver and peripheral tissues to carbon dioxide and water [5]. The rate limiting step in the ADH pathway is the limited availability of NAD+ thus alcohol metabolism is restricted to approximately 15g per hour [1]. A secondary oxidation pathway for alcohol metabolism is the microsomal alcohol oxidising system (involving microsomal cytochrome P450 (CYP) 2E1), which due to its low affinity (Km ~ 10mM) for alcohol (about 10 fold lower than ADH) only accounts for ~10 % of total alcohol clearance by the liver at low concentrations [11, 2]. However, at higher BAC the increased activity of this pathway could account for the observed increase in the rate of alcohol metabolism above 0.065 % BAC (16). Also, unlike the ADH pathways CYP2E1 is induced after prolonged heavy alcohol intake [1, 11, 16], but is inhibited by short-term binge drinking [11]. This accounts for some of the interactions observed between alcohol and other drugs which are also metabolised via this pathway [11, 16]. The other potentially harmful consequences of CYP2E1 induction are increased vitamin metabolism (e.g. retinol) and the increased production of reactive oxygen species (ROS) [1]. A third oxidative pathway via the heme enzyme catalase also exists, which converts a small proportion of alcohol (0-2%) to acetaldehyde and water [10, 2]. The consequences of alcohol metabolism contribute to the detrimental consequences of alcohol. For example, the alteration in metabolism produced by alcohol increases oxygen requirements of hepatocytes resulting in hypoxia in poorly perfused areas of the liver [15]. This, combined with increased production of ROS and interactions of alcohol by-products with cell components cause damage in liver tissues [15]. Chronic misuse therefore results in tissue injury such as hepatomegaly and liver cirrhosis.

Non-oxidative pathways of alcohol metabolism also exist. Although the metabolism of alcohol by these pathways is minimal the products may have pathological relevance because their products persist after alcohol elimination and have been demonstrated to interfere with cell signalling [15]. However, their role in alcohol-induced disease remains to be fully elucidated.
The rate of alcohol metabolism is influenced by the BAC and genetics via the particular ADH isoenzymes present in the individual. The rate of alcohol metabolism is exponential below a blood alcohol concentration of approximately 0.02 %, above this level ADH becomes saturated resulting in a relatively constant metabolism rate (zero order kinetics) between BAC of ~ 0.020 and 0.065% [10]. The rate of metabolism increases as the BAC increases above 0.065 % possibly due to the greater activity of CYP2E1 [16]. An individual’s genetics can also influence the pharmacokinetics of alcohol. At least four different isoenzymes of ADH exist and each has a different affinity for alcohol [5], which will affect the overall rate of alcohol metabolism. Several isoenzymes of aldehyde dehydrogenase also exist, which can lead to some ethnic groups producing adverse reactions to alcohol. Approximately 50% of Japanese people are missing one kind of aldehyde dehydrogenase isoenzyme which produces unpleasant symptoms associated with drinking [5]. Symptoms include flushing, nausea, and vomiting, palpitations and throbbing headache, believed to be caused by the accumulation of acetaldehyde. Interestingly Disulfiram (Antabuse®) an adjuvant drug used in the treatment of chronic alcohol dependence utilises a similar mechanism. Disulfiram interferes with aldehyde dehydrogenase increasing acetaldehyde levels causing unpleasant reactions to alcohol consumption [17]. This may partly explain the low levels of alcohol dependency observed in Asian-Americans compared with other ethnic groups [18].

Gender differences in alcohol metabolism and elimination have also been suggested following a number of studies which demonstrated increased rates of alcohol elimination in females compared with males (see Mumenthaler et al [10] for review). It has been proposed that this difference is due to the higher maximum BAC in females activating the CYP2E1 system to clear more alcohol, but comparison of comparable maximum BAC between males and females still demonstrated higher clearance rates in women [10]. Other investigations have looked at the influence of hormones on clearance rates. Lower rates in males may be linked to the finding that the reproductive hormone dihydrotestosterone inhibits hepatic ADH activity (in rats) [19, 20]. Whereas higher clearance rates in females may be linked to the action of oestrogen (e.g. in pregnancy or due to the oral contraceptive pill) as increased levels have been found to increase hepatic ADH activity [5, 10]. Further research is required to clarify the role that hormone levels play in gender differences in alcohol pharmacokinetics.

Conclusion(s)

Alcohol is the most widely used drug worldwide and has important implications for public health. Large intraindividual and interindividual differences in alcohol pharmacokinetics exist and numerous factors are responsible for producing these differences. Knowledge of these factors and their influence on alcohol absorption, distribution, metabolism, and excretion is important to understand alcohol's physiological effects, drug interactions, and pathological consequences.

References

10. Mumenthaler MS, Taylor JL, O'Hara R, Yesavage JA. Gender differences in moderate drinking effects.
Illustrations

Illustration 1

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Differences in TBW &amp; ?gastric ADH</td>
</tr>
<tr>
<td>Age</td>
<td>Changes in TBW</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Different sensitivities to alcohol</td>
</tr>
<tr>
<td>Weight/BMI</td>
<td>Influences TBW</td>
</tr>
<tr>
<td>Hormone levels</td>
<td>Differences in elimination rates (e.g. pregnancy)</td>
</tr>
<tr>
<td>Drinking pattern</td>
<td>Tolerance to alcohol</td>
</tr>
<tr>
<td>Type of alcohol</td>
<td>Amount &amp; strength can affect absorption</td>
</tr>
<tr>
<td>Mixer</td>
<td>Can affect absorption</td>
</tr>
<tr>
<td>Time to drink</td>
<td>Affects peak BAC and time to peak BAC</td>
</tr>
<tr>
<td>Stomach content</td>
<td>Timing &amp; meal type (e.g. fat content) affect absorption</td>
</tr>
</tbody>
</table>

TBW = Total Body Water; ADH = Alcohol Dehydrogenase; BMI = Body Mass Index. Table adapted from Breslin et al [21].
Factors affecting gastric emptying.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach contents</td>
<td>Food inhibits absorption</td>
</tr>
<tr>
<td>Alcohol content</td>
<td>Absorption quickest between 20-30 %</td>
</tr>
<tr>
<td>Alcohol exposure &amp; tolerance</td>
<td>Gastric emptying is ↑ with ↑ tolerance to alcohol</td>
</tr>
<tr>
<td>ANS</td>
<td>SNS ↓ &amp; PNS ↑ gastric emptying</td>
</tr>
<tr>
<td>Drugs</td>
<td>Can ↑ or ↓ gastric emptying</td>
</tr>
<tr>
<td>Carbonated drinks</td>
<td>↑ the rate of absorption</td>
</tr>
</tbody>
</table>
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