



Absorption and Peak Blood Alcohol Concentration After Drinking Beer, Wine, or Spirits

Mack C. Mitchell Jr., Erin L. Teigen, and Vijay A. Ramchandani

Background: Both the amount and the rate of absorption of ethanol (EtOH) from alcoholic beverages are key determinants of the peak blood alcohol concentration (BAC) and exposure of organs other than gut and liver. Previous studies suggest EtOH is absorbed more rapidly in the fasting than in the postprandial state. The concentration of EtOH and the type of beverage may determine gastric emptying/absorption of EtOH.

Methods: The pharmacokinetics of EtOH were measured in 15 healthy men after consumption of 0.5 g of EtOH/kg body weight. During this 3-session crossover study, subjects consumed in separate sessions, beer (5.1% v/v), white wine (12.5% v/v), or vodka/tonic (20% v/v) over 20 minutes following an overnight fast. BAC was measured by gas chromatography at multiple points after consumption.

Results: Peak BAC (C_{max}) was significantly higher ($p < 0.001$) after vodka/tonic (77.4 ± 17.0 mg/dl) than after wine (61.7 ± 10.8 mg/dl) or beer (50.3 ± 9.8 mg/dl) and was significantly higher ($p < 0.001$) after wine than beer. The time to C_{max} occurred significantly earlier ($p < 0.01$) after vodka/tonic (36 ± 10 minutes) compared to wine (54 ± 14 minutes) or beer (62 ± 23 minutes). Six subjects exceeded a C_{max} of 80 mg/dl after vodka/tonic, but none exceeded this limit after beer or wine. The area under the concentration-time curve (AUC) was significantly greater after drinking vodka/tonic ($p < 0.001$) than after wine or beer. Comparison of AUCs indicated the relative bioavailability of EtOH was lower after drinking beer.

Conclusions: Findings indicate that BAC is higher after drinking vodka/tonic than beer or wine after fasting. A binge pattern is significantly more likely to result in BAC above 80 mg/dl after drinking vodka/tonic than beer or wine. Men drinking on an empty stomach should know BAC will vary depending on beverage type and the rate and amount of EtOH.

Key Words: Alcohol Absorption, Pharmacokinetics, Beverage Type Differences, Blood Alcohol Concentrations, Gastric Emptying Rate.

BECAUSE THE RATE of absorption of ethanol (EtOH) is greater than its rate of elimination, both the amount of EtOH consumed and the rate of absorption of alcoholic beverages are key determinants of the peak blood alcohol concentration (BAC) (Holt, 1981; Ramchandani et al., 2001a; Wilkinson et al., 1977). The rate of

elimination of EtOH is determined largely by the activity of hepatic alcohol dehydrogenases (ADH), the primary enzymes that metabolize EtOH. ADH are saturated at relatively low concentrations of EtOH leading to a rate of elimination that is sometimes described as zero-order kinetics at higher concentrations and pseudo-linear or first-order at concentrations below the saturation of ADH (Wilkinson et al., 1977). Absorption of EtOH continues over a prolonged period of time after ingesting alcoholic beverages, with BACs continuing to increase until the rate of elimination exceeds the rate of absorption. For these reasons, the rate of absorption is a primary determinant of the peak BAC. As most of the effects of EtOH are related to the BAC, variables that influence the rate of absorption are of interest. EtOH is absorbed more rapidly during the fasting than the fed state (DiPadova et al., 1987; Horowitz et al., 1989; Jones, 2000; Roine et al., 1993). Furthermore, solid meals delay gastric emptying more so than liquid meals, and the rate of absorption of EtOH consumed with a solid meal is likewise slower than when consumed with a liquid meal, probably as a function of the rate of gastric emptying (Horowitz et al., 1989). Other studies indicate that food increases the rate of elimination of EtOH (Ramchandani et al., 2001b).

During both the fasting and fed states, the rate of absorption of alcoholic beverages is influenced by the

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concentration of EtOH in the beverage (Mellanby, 1919; Roine et al., 1993; Wilkinson et al., 1977). Previous studies reported variable results depending on the concentration of alcohol in the beverage. Some studies reported that higher concentration of alcohol in a beverage delays the rate of gastric emptying particularly after a meal (Haggard et al., 1941; Roine et al., 1991; Sedman et al., 1976). Many of these studies utilized 95% EtOH diluted to different concentrations in orange juice or water, although some used beer, wine, and spirits (both diluted and neat) during or after a standard meal. Other studies have reported that during the fasting state, dilute alcoholic beverages such as beer are absorbed more slowly than beverages with a high EtOH concentration such as whiskey (Mellanby, 1919; Roine et al., 1993).

Alcoholic beverages are consumed in a variety of situations, including with meals and at social gatherings where food may or may not be consumed with the beverages. In bars and taverns, alcoholic beverages are often consumed in the absence of food or several hours after eating, at which time the stomach is empty or nearly so. These social settings more closely resemble the fasting condition than drinking with meals. The purpose of this study was to determine during the fasting state, the kinetics of alcohol absorption and elimination and peak BACs after drinking the same amount of EtOH in the form of beer (5.1% v/v), white table wine (12.5% v/v), and vodka (diluted to 20% v/v with tonic water).

MATERIALS AND METHODS

Subjects

Fifteen healthy, nonsmoking men between the ages of 25 to 65 were selected for participation after responding to an advertisement. Subjects were screened for underlying medical conditions through a standardized history and physical examination and routine chemistry and hematological tests. The Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire was used to evaluate subjects for possible alcohol-use disorders. Lifetime abstainers from alcohol and subjects with a score > 4 on the AUDIT-C, evidence of hypertension (blood pressure > 150/90), liver disease (including positive testing for hepatitis B or C), kidney disease, HIV infection, or other chronic illnesses based on history or biochemical parameters or hematological parameters were excluded from participation. Subjects with a body mass index (BMI) > 30 or < 18.5 were excluded. Subjects who were on any medications except occasional over-the-counter medications were excluded. Surreptitious smoking was evaluated by screening subjects with urine cotinine. Any subject with urine cotinine > 200 ng/ml was excluded.

Urine drug screens were performed at time of screening and on admission to the clinical research unit. A total of 66 men were screened to identify the 15 who participated in the study. The vast majority failed screening due to high AUDIT-C scores. Three participants were of European descent, 9 were African American, and 3 were Hispanic. The mean age of subjects was 37.8 years (range 26 to 55). The mean weight was 82.66 kg (range 68.6 to 96.4), and mean BMI was 26.35 (range 21.9 to 29.9).

Study Protocol

Subjects were required to abstain from alcoholic beverages for 48 hours prior to the study and to abstain from taking any over-the-counter or prescription medications including vitamins, with the exception of acetaminophen (< 1000 mg/d) for 14 days before the study. Subjects were admitted to the clinical research unit the day before the studies and remained as inpatients throughout the 3 days of study. The night before each study session, they were fed a standardized meal that was similar in composition on each of the days. Each subject was assigned a number, and all data were analyzed without personal identification. Subjects were monitored for adverse events throughout the entire period of the study from admission to discharge from the clinical research unit.

Administration of Alcoholic Beverages

Alcoholic beverages (0.5 g EtOH/kg body weight) were consumed over a 20-minute period beginning at 8 AM following an overnight fast. The volume of the alcoholic beverage was divided, so that half of the beverage was consumed within the first 10 minutes and the remainder within the next 10 minutes. Beer (5.1% v/v), white table wine (Chardonnay, 12.5% v/v), or vodka mixed with regular tonic to achieve a final concentration of 20% v/v was administered in a randomized fashion, so that 5 subjects received beer on day 1, 5 received wine on day 1, and 5 received vodka/tonic on day 1. The order of administration of the other beverages was also randomized on days 2 and 3. After a 20-minute period of consumption of the alcoholic beverages, the subjects remained fasting for 4 hours at which time they were allowed to eat a light lunch. All subjects completed each of the 3 beverage studies.

Blood Sampling

Venous blood samples were drawn from an indwelling catheter at specified times after administration of alcoholic beverages: Baseline, 10, 20, 30, 40, 60, 90, 120, 150, 180, 210, 240, 360, 480 minutes.

Analysis of Blood Ethanol

Whole BACs were analyzed at Mayo Laboratories (Rochester, MN) using head-space gas chromatography.

Pharmacokinetics Analysis

Noncompartmental analysis of individual concentration-time profiles was used to estimate the following pharmacokinetic (PK) measures:

- Peak concentration (C_{\max})
- Time to peak concentration (T_{\max})
- Area under the concentration-time curve (AUC): The AUC is a measure of exposure that integrates concentration across time. AUC was calculated using trapezoidal rule up to the last measured time point and was not extrapolated (using the typical linear extrapolation) due to the nonlinear PKs of alcohol.
- Mean residence time (MRT): The average time that drug remains in the body after administration (a time-based measure of exposure) was calculated as $AUMC/AUC$, where AUMC is the area under the moment curve, calculated from the concentration-time moment curve (concentration \times time vs. time) using the trapezoidal rule.
- Apparent clearance (CL_{app}) calculated as Dose/AUC.
- Volume of distribution (V_{ss}) = $MRT \times CL_{app}$
- Relative bioavailability: The relative bioavailability of alcohol following wine relative to spirits ($F_{W/S} = \frac{AUC_W \times Dose_S}{AUC_S \times Dose_W}$) and the

relative bioavailability of alcohol following beer relative to spirits ($F_{B/S} = \frac{AUC_B \times Dose_B}{AUC_S \times Dose_B}$) were estimated as measures of relative exposure following the beverages.

Statistical Analysis

Individual PK measures for each subject were tabulated and compared across sessions using repeated-measures analysis of variance (SPSS version 20.0; IBM, Armonk, NY). The level of statistical significance was set to 0.05. In case of significant differences, post hoc comparisons between sessions were performed using paired *t*-tests.

RESULTS

Figure 1 shows the geometric mean (\pm SD) BAC for all subjects versus time. As the profile indicates, the peak BAC was higher after consumption of vodka/tonic than wine or beer. The time required to reach the peak BAC was also earlier following vodka/tonic compared with wine or beer.

Analysis of PK parameters indicated statistically significant differences among beverage types for C_{max} , T_{max} , and AUC (Table 1). Statistical analysis using post hoc *t*-tests showed significant differences between all beverage pairs compared, such that the spirits (vodka/tonic) session showed the highest peak concentration and AUC, followed by wine and then by beer. The time to peak concentration was significantly shorter for spirits compared to wine and beer, while time to peak concentration did not differ significantly between wine and beer. MRT was shortest for spirits followed by wine and then by beer. These results indicate that spirits resulted in higher exposure compared to wine and beer, while beer resulted in lower and delayed exposure compared to spirits and wine.

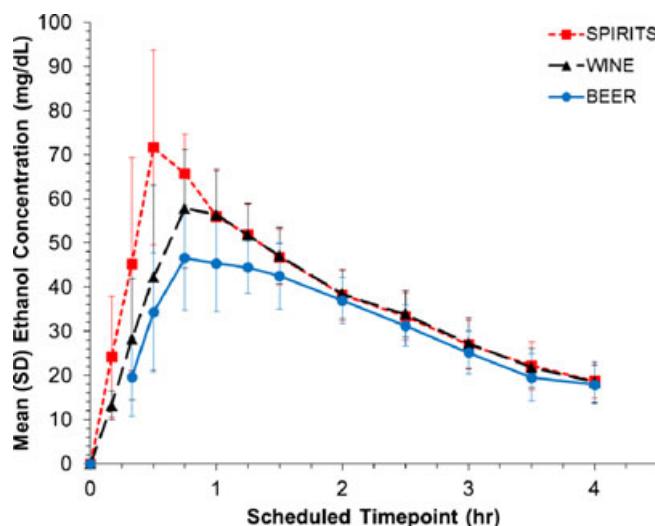


Fig. 1. Geometric mean values for blood alcohol concentrations following consumption of vodka/tonic (red squares), wine (black triangles), or beer (blue circles) are shown over time. Time zero represents initiation of consumption of beverages that was complete within 20 minutes.

The relative bioavailability for wine and beer relative to spirits was estimated from the AUC and adjusted for the absolute dose (in grams) administered. The estimated bioavailability for wine relative to spirits was 0.96 ± 0.13 (SE) and was not significantly different from the theoretical value of 1 for bioequivalent formulations. The estimated bioavailability of beer relative to spirits was 0.90 ± 0.02 (SE) and was significantly lower than the theoretical value of 1 for bioequivalent formulations. This finding implies that there is a 10% reduction in bioavailability of alcohol when administered as beer compared to spirits. Apparent clearance and volume of distribution showed higher values for beer compared to spirits or wine, probably resulting from the lower relative bioavailability of alcohol following wine and beer compared to spirits (Table 1).

In 14 of 15 subjects, the rate of absorption of spirits was greater than wine or beer. In 7 of the 15 subjects, the peak BAC exceeded 80 mg/dL (0.08%) after drinking vodka/tonic compared to beer or wine, and in 4 subjects, the peak BAC after vodka/tonic was more than 2-fold higher than after drinking beer. Peak BAC remained below 80 mg/dL in all subjects after consumption of this amount of beer or wine.

DISCUSSION

Our results show clearly that beer and wine are absorbed more slowly than vodka/tonic and that the peak BAC after drinking beer is significantly lower than the peak BAC after drinking a similar amount of EtOH as wine or vodka/tonic. The peak BAC after drinking wine was also significantly lower than after drinking vodka/tonic. In addition, the overall BAC exposure (AUC) following beer was lower than that for wine or vodka/tonic, which suggest a lower relative bioavailability for beer compared to the other beverages. While the estimated clearance for beer appears to be higher than that obtained for the other beverages, it is an “apparent” estimate because the route of administration is nonsystemic and artificially inflated as a result of the lower C_{max} and bioavailability for beer. Similarly, the apparent volume of distribution does appear to differ across beverages; however, this too may be confounded by the differences in bioavailability across the beverage types.

The beverages used in this study differ in both the concentration of EtOH and the caloric content of the beverages. The concentration of alcohol in beer was 5.1% v/v, wine was 12.5% v/v, and vodka was diluted to a concentration of 20% v/v in tonic. Thus, the concentration of EtOH in vodka/tonic (20%) was almost twice that of wine (12.5%) and 4 times the concentration of beer. Although this study was not designed to test the effect of concentration of alcoholic beverages directly, the findings suggest that, in the fasting state, less concentrated beverages such as beer and wine are absorbed more slowly than those that are more concentrated. Previous studies have not shown a consistent effect of concentration on the rate of absorption from different alcoholic beverages (Mellanby, 1919; Roine et al., 1993;

Table 1. Pharmacokinetic Parameters After Spirits, Wine, or Beer

PK Measure	Spirits	Wine	Beer	p-Value
C _{max} [mg%]	77.4 (17.0)	61.7 (10.8)	50.3 (9.8)	F(2,28) = 30.757, p < 0.001 t-tests: Spirits > Wine > Beer
T _{max} [hour]	0.6 (0.2)	0.9 (0.2)	1.0 (0.4)	F(2,28) = 12.103, p < 0.001 t-tests: Spirits > Wine = Beer
AUC _t [mg*h/l]	1,510.9 (216)	1,379 (219.9)	1,193.6 (184.1)	F(2,28) = 22.082, p < 0.001 t-tests: Spirits > Wine > Beer
MRT [hour]	1.7 (0.2)	1.8 (0.3)	1.8 (0.2)	F(2,28) = 3.968, p = 0.030 t-tests: Spirits = Wine > Beer
CL _{app}	27.7 (3.6)	29.4 (5.3)	31.0 (4.2)	F(2,28) = 6.527, p = 0.005 t-tests: Spirits = Wine < Beer
VD _{app}	46.3 (7.5)	51.7 (8.3)	56.6 (8.9)	F(2,28) = 14.291, p < 0.001 t-tests: Spirits < Wine < Beer

Results of post hoc *t*-tests are shown to compare results among the 3 conditions (spirits, wine, or beer). Values shown are the mean with standard error in parentheses.

PK, pharmacokinetics measure; C_{max}, peak blood alcohol concentration; T_{max}, time to peak concentration; AUC, area under the concentration-time curve; MRT, mean residence time; CL_{app}, apparent clearance; VD_{app}, volume of distribution.

Wilkinson et al., 1977). Both the caloric content and other minor constituents of beer, wine, or vodka/tonic could potentially influence the rate of absorption. Although the calories from EtOH in each beverage were constant, beer has more total calories than either wine or vodka/tonic due to the carbohydrate content. An 80 kg subject would have ingested 409 calories as beer, 334 calories as wine, and 297 calories as vodka/tonic. The caloric content of beer could play a role in our findings because gastric emptying is influenced by the calories ingested more than the composition of the meal (Calbet and MacLean, 1997; Velchik et al., 1989). However, the differences in peak BAC between wine and vodka/tonic which have similar caloric value suggest that concentration is a more important determinant of the rate of gastric emptying and/or absorption of EtOH. Our findings do not permit a way to evaluate the effects of minor components of the beverages.

The findings in this study confirm previous observations that alcoholic beverages are absorbed rapidly during the fasting state, reaching a peak BAC within 1 hour (Jones, 2000; Roine et al., 1993; Wilkinson et al., 1977). We observed that the peak BAC occurred much sooner after consumption of vodka tonic (0.60 ± 0.17 hours) than after drinking wine (0.91 ± 0.23 hours) or beer (1.04 ± 0.38 hours). This finding is internally consistent with differences in the rate of absorption of EtOH from beer, wine, or vodka/tonic.

EtOH is well absorbed by the intestinal mucosa (Gentry, 2000). As portal venous blood first passes through the liver before reaching the systemic circulation, the liver is exposed to most of the EtOH that is ingested. The liver is the primary site of metabolism of EtOH. Previous studies have shown that the bioavailability of EtOH is < 1 for very low doses of EtOH suggesting a possible "first-pass" effect (Gentry, 2000; Wilkinson et al., 1977). This effect is saturated at relatively low doses and thus would not apply to our findings. However, if alcoholic beverages are consumed and/or absorbed at a rate that is lower than the rate of metabolism and elimination by the liver, the amount of EtOH reaching target organs such as the brain would be negligible. The AUC reflects aggregate exposure of organs other than the liver to EtOH following ingestion

of alcoholic beverages. The AUC after consumption of beer was significantly lower (geometric mean 160.9) than after consumption of wine (177.5) or vodka/tonic (196.8). This finding suggests that the exposure of organs such as the brain to EtOH may be lower after drinking equivalent amounts of EtOH in the form of beer compared to wine or vodka/tonic in the fasting state. Although a different amount of EtOH (0.3 g/kg body weight) was ingested, Roine and colleagues (1993) reported similar findings in AUC for beer, wine, and undiluted whiskey (40%) when consumed in the fasting state.

These findings have implications for individuals who consume alcoholic beverages in the absence of food. Drinking more concentrated beverages such as vodka/tonic is highly likely to produce higher peak BAC than when the same amount of EtOH is consumed as beer or wine. Although 12 ounces of beer, 5 ounces of wine, and 1.5 ounces of liquor (80 proof) contain approximately the same amount of EtOH, the peak BAC and the aggregate exposure to EtOH of organs other than the liver and gut may differ significantly depending on the type of alcoholic beverage and the rate at which it is consumed. Rapid consumption of alcoholic beverages, particularly those that are highly concentrated, in the absence of food, should be discouraged.

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The relationship between alcohol elimination rate and increasing blood alcohol concentration—Calculated from two consecutive blood specimens

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Abstract

In the period 1991–2005, a blood-alcohol concentration (BAC) analysis was carried out at the Institute of forensic medicine in Novi Sad including 2023 two consecutive blood specimens using the Headspace Gas Chromatography method. Cases with no alcohol concentration values, as well as cases where blood samples were taken within 1 h after the criminal act, were not taken into consideration. Following this rule, 1198 cases were considered in this study and all samples were grouped in 29 ranges of BAC_1 of $\Delta_{BAC} = 0.1$ g/kg, starting from 0.1–0.19 g/kg to 2.9–2.99 g/kg of absolute alcohol.

Gathered results and elimination curve differ from the zero-order model of elimination proposed by Widmark and point to an elimination process similar to a well-known Michaelis-Menten elimination kinetics model and its variants. Results reported in this study show dependence of alcohol elimination rate (β -slope) and BAC value. The analysis of β_{60} -slope versus BAC shows that a correlation between β_{60} (y) and BAC (x) has a logarithmic trend line. The value of alcohol elimination rate shows a slight increment with increase of BAC alcohol, with the mean value of $\beta_{60} = 0.221 \pm 0.075$ g/kg. Differences in values of β_{60} among consecutive intervals of $\Delta_{BAC} = 0.1$ g/kg are not significant ($p > 0.05$). When obtained samples were grouped into ranges of 0.5 g/kg each in these intervals β_{60} had the following values by range: 0.1–0.49 g/kg = 0.139 g/kg \pm 0.035; 0.5–0.99 g/kg = 0.184 g/kg \pm 0.043; 1–1.49 g/kg = 0.213 g/kg \pm 0.052; 1.5–1.99 g/kg = 0.239 g/kg \pm 0.058; 2–2.49 g/kg = 0.265 g/kg \pm 0.073; 2.5–2.99 g/kg = 0.306 g/kg \pm 0.096. Differences in values of beta slope among consecutive intervals of $\Delta_{BAC} = 0.5$ g/kg are significant ($p < 0.01$).

The elimination curve in the BAC interval 0.5–2.5 g/kg has a linear trend, while beta-slope (y)/BAC (x) correlation is given as $\beta_{60} = 0.15$ g/kg + (0.05 g/kg \times BAC).

Retrograde calculation of the blood alcohol concentration in *tempore criminis* (BAC_{tc}) based on the determined alcohol concentration in the blood specimen (BAC_t) shows a statistically significant difference between BAC_{tc} calculated using a standard zero-order model versus corrected methodology. The higher the BAC_t and the longer the calculation time, the greater and statistically more significant ($p < 0.01$) is the difference between the calculated values of BAC_{tc} .

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Keywords: Forensic medicine; Ethanol disappearance; Alcohol elimination; Disappearance rate (β -slope)

1. Introduction

Systematic research has already confirmed that alcohol is a significant cause not only of traffic accidents, but also of many other types of accidents and criminal acts. Forensic pathologists and toxicologists act in such cases as expert witnesses,

with the task of determining blood alcohol concentration in “*tempore criminis*” (BAC_{tc}), either in retrograde manner, or on the basis of the dynamics of alcohol consumption. In our country BAC is calculated using the generally accepted Widmark equation and constant elimination rate – zero-order model (β_{60} -slope of 0.15 g/kg), regardless of the initial BAC, although the limitations of this model have been known for a long time.

A frequent occurrence of a phenomenon known in court practice as hip-flask defense, to us known as “cognac alibi” defense model [1], has led to establishing a practice of taking

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two blood samples from perpetrators of criminal acts within 60 min apart.

The results of the analyses indicated that there were no standard values for β -slope per hour. Some counsels adapted to this fact and, depending on whether it is more convenient for the defendant to have a lower (in traffic accidents) or higher alcohol concentration (in murder cases, for example) they usually ask the expert witness to use standard β -slope in one case, and in another the one obtained by analysis, arguing that this value is a fact. Such differences in approach, to which forensic medicine experts have objected more or less successfully, cause confusion in court and at the same time, disobey the principle of equality of citizens in the court of law.

These facts have influenced our decision to analyze the 15-year data, i.e. the values of β -slope in cases where two blood samples were taken.

2. Material and methods

Following a strict protocol, the blood samples were collected at the same location, at the Department of emergency medicine of the Clinical Center in Novi Sad, Serbia. The specimens (3 mL of blood) were collected directly into plastic tubes containing 30 mg of sodium fluoride. Each tube was marked with an identification code, sealed, properly stored and sent to the Toxicology Laboratory of the Institute of forensic medicine. A police voucher accompanied every specimen, containing the name of the suspect, time of arrest and time of blood sampling. The police kept the suspects under constant surveillance, from the time of arrest to the time of blood sampling. Therefore, consumption of alcohol after arrest was practically impossible.

In the period 1991–2005, in 2023 cases two consecutive blood specimens' analyses were performed at the Institute of forensic medicine in Novi Sad. Two blood specimens were taken from each suspect with a 30–60 min interval. The cases with no alcohol concentration values, as well as cases where blood samples were taken too soon (within 1 h) after the criminal act, were not taken into consideration. Following this rule, 1198 cases were considered in this study.

Blood analyses were performed using an exact and precise methodology—Headspace Gas Chromatography (*Hewlett Packard*). Data on blood alcohol concentration at first (BAC₁) and second sampling (BAC₂), the time of first (t_1) and second (t_2) blood sampling were analyzed.

In 84% of cases ($N = 1005$) the second sample was taken within 60 min. The apparent alcohol elimination rate was calculated using the following formula:

$$\beta_{60} = \text{BAC}_1 - \text{BAC}_2.$$

In 16% of cases ($N = 193$) the second sample was taken 30–59 min later, and the elimination rate (β -slope) was calculated using the following formula:

$$\beta_{60} = (\text{BAC}_1 - \text{BAC}_2) \times \left[\frac{60}{t_2 - t_1} \right].$$

Statistical analysis was performed by calculating mean values of alcohol concentration, standard deviation and median within 0.1 g/kg and 0.5 g/kg intervals.

3. Results

The calculated blood alcohol concentration in the first sample (BAC₁) was between 0.1 g/kg and 2.99 g/kg of absolute alcohol, with the mean of 1.442 g/kg, whereas in the second sample (BAC₂) it was 1.227 g/kg. All samples were grouped in 29 ranges of BAC₁ of 0.1 g/kg, starting from 0.1–0.19 g/kg to 2.9–2.99 g/kg. The arithmetic mean value (Fig. 1) and standard

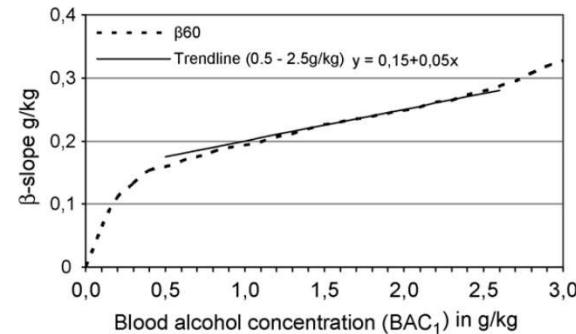


Fig. 1. Mean values of β_{60} -slope within the range of 0.1 g/kg per group (dashed), and linear trend line for interval 0.5–2.5 g/kg (continual line).

deviation of the alcohol elimination rate were calculated for each group. The β -slope value ranged between 0.054 g/kg and 0.648 g/kg, depending on the BAC with the mean value of 0.221 g/kg \pm 0.075 (S.D.).

Apart from that, all samples were sorted into six additional groups within 0.5 g/kg of blood alcohol concentration range. The mean value, standard deviation and median of the alcohol elimination factor were calculated for each group (Table 1).

It is shown on the alcohol elimination curve that there is a linear beta-slope increase in the 0.5–2.5 g/kg interval. Data analysis in this interval has shown that correlation between beta-slope (y) and BAC₁ (x) has the following relationship: $y = 0.15 + 0.05x$ (Fig. 1), i.e.:

$$\beta_{60} = 0.15 \text{ g/kg} + (0.05 \text{ g/kg} \times \text{BAC}).$$

In other words, for any increase of the BAC value by $\Delta_{\text{BAC}} = 0.1 \text{ g/kg}$ beta-slope averagely increases by $\Delta_{\beta_{60}} = 0.005 \text{ g/kg}$.

According to presented data, it could be concluded that if there is an β_{60} increase depending on BAC increase, the elimination time needed for $\Delta_{\text{BAC}} = 0.1 \text{ g/kg}$ is not always the same, but decreases with increased BAC, which could be described by the following equation:

$$\Delta_t = \frac{0.1 \text{ g/kg}}{0.15 \text{ g/kg} + (0.05 \text{ g/kg} \times \text{BAC}_t)}.$$

Calculated Δ_t values in different BACs in 0.1 g/kg intervals are shown in Fig. 2. It is shown that correlation between Δ_t (y) and BAC₁ (x) has a linear trend:

$$\Delta_t = 0.6 - 0.1 \times \text{BAC}_1.$$

Table 1
Values of β_{60} -slope within range of 0.5 g/kg per group

BAC range (g/kg)	Number of cases	Mean value (g/kg)	S.D.	Median (g/kg)
<0.5	147	0.139	0.035	0.142
0.5–0.99	229	0.184	0.043	0.181
1.0–1.49	226	0.213	0.052	0.206
1.5–1.99	261	0.239	0.058	0.235
2.0–2.49	185	0.265	0.073	0.249
2.5–2.99	110	0.306	0.096	0.279
0.1–2.99	1198	0.221	0.075	0.209

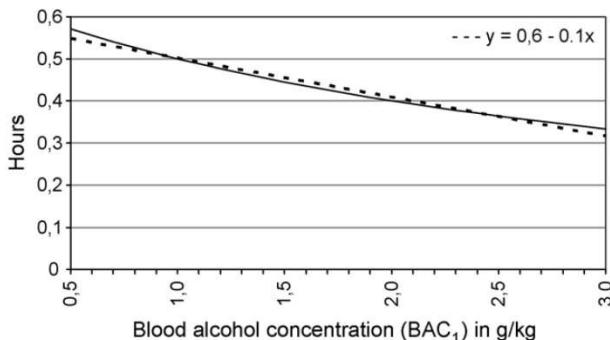


Fig. 2. Elimination time within the range of 0.1 g/kg in different values of BAC.

4. Discussion

The use of the generally accepted zero-order model of ethanol elimination, first proposed by Widmark in forensic expertise, has been routinely applied, although the limitations of this model have been known for a long time.

Previous researches of the pharmacokinetic disposition of ethanol metabolism in biological systems were mainly based on experiments on both humans [2–14] and animals [15–17]. Mean values differed both in animals and humans, depending on the quantity of alcohol intake by kilogram of body mass and way of application (ingestion versus intravenous injection). Discrepancies in reported results clearly show a difference in alcohol elimination as a function of BAC, although they are closer to Widmark's mean values in studies performed on human subjects, probably because smaller quantities of alcohol were used in experiments (mostly 0.5–1 g/kg of body mass).

Results reported in this study show dependence of β -slope and BAC value. The curve shape is similar to the non-linear pharmacokinetic curve, which has a mathematic interpretation proposed by Michaelis-Menton [18] equation for enzyme kinetics. The analysis of alcohol elimination rate (β_{60}) versus BAC shows a hyperbolic shape plot. A correlation between beta-slope (y) and BAC (x) has a logarithmic trend line (Fig. 3). This is especially true for elimination of lower alcohol concentration from blood (BAC up to 0.5 g/kg), where a significant difference ($p < 0.05$) between intervals of 0.1 g/kg has been established. Above this value, differences in values of

alcohol elimination rates among consecutive intervals are not significant ($p > 0.05$). The beta slope shows a slight increment with increase of BAC, which was also confirmed by other researchers [10]. When obtained samples were grouped into ranges of $\Delta_{\text{BAC}} = 0.5 \text{ g/kg}$ (Table 1) differences in values of beta slope among consecutive intervals are significant ($p < 0.01$).

Large studies on alcohol elimination using the two blood sample method are scarce. A major limitation of this method is that the validity of results depends on the liability and accuracy of persons registering the time of sampling, which opens the question of sampling validity. However, a great number of samples minimize possible errors. The next weak point of this kind of study is that at the time of first sample taking the examinee may still be in the phase of absorption of previously consumed alcohol. In order to exclude such cases, we analyzed only cases where at least one hour passed from the time of alcohol consumption and blood sampling. Nevertheless, we cannot exclude the possibility that some suspects did not fully enter the elimination phase at the time of blood sampling. In other words, they might be considered as being in the plateau phase of the BAC profile versus time curve, which is the case in subjects who consume great quantities of food with drinks of lower alcohol concentration.

In the Netherlands, an analysis was carried out by Neuteboom and Jones [19] using the two consecutive blood sample method in 1314 drunken drivers. The reported mean alcohol elimination rate was 0.22 mg/mL/h, which is not different from mean values obtained in our study ($\beta_{60} = 0.221 \text{ g/kg}$). In the study of 1090 double blood samples, Jones and Andersen [20] found an overall mean alcohol elimination rate of 0.191 mg/mL/h, while other researchers reported lower mean values: Lund [21]—mean value of 17 mg/mL/h, and in several German studies [22] based on double blood sampling, the mean value of alcohol elimination rate was 0.18 mg/mL/h.

Using a capacity-limited model, similar to the Michaelis-Menton model for enzyme kinetics, Holford [23] calculated the maximum rate of ethanol elimination of 8.5 g/h/70 kg—equivalent to the blood ethanol elimination rate of 230 mg/L/h, while Wilkinson et al. [24] found the average V_{\max} of 0.232 mg/mL/h. This is in concordance with the mean value reported in our study.

Our study, as well as other published reports, shows that the value of the elimination parameter per hour may be extremely high: in small number of cases it was 0.4–0.6 g/kg/h, and the maximal reported value was 0.648 mg/mL/h, whereas higher rates seem to be associated with higher initial BAC. Generally speaking, significant variations were found in alcohol elimination rates within one range of BAC of 0.1 g/kg, for example in BAC₁ 1.4–1.49 g/kg the value of β_{60} -slope ranged 0.14–0.353 g/kg.

Studies of ethanol pharmacokinetics show that there are numerous factors affecting alcohol elimination [25]. In a number of papers, sex differences in blood alcohol elimination rate have been reported. Experiments conducted by Taylor et al. [12] and by Seidl et al. [26] showed faster alcohol elimination

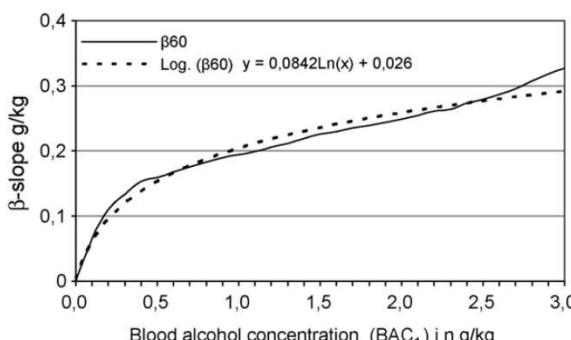


Fig. 3. Mean values of β_{60} -slope within the range of 0.1 g/kg per group (continuous line), and trend line (dotted).

Table 2

Comparison of the retrograde calculated BAC_{tc} vs. $\beta_{60} = 0.15 \text{ g/kg}$ (row a), $\beta_{60} = 0.15 \text{ g/kg} + 0.05 \text{ g/kg} \times \text{BAC}$ (row b), with corrected factor of time (Δ_t) needed for elimination of $\Delta_{\text{BAC}} = 0.1 \text{ g/kg}$ (row c)

BAC_t (g/kg)		BAC_{tc} g/kg vs. time (h)											
		0^{15}	0^{30}	0^{45}	1^{00}	1^{15}	1^{30}	1^4	2^{00}	2^{15}	2^{30}	2^{45}	
0.5	a	0.538	0.575	0.613	0.650	0.688	0.725	0.763	0.800	0.838	0.875	0.913	0.950
	b	0.544	0.588	0.631	0.675	0.719	0.763	0.806	0.850	0.894	0.938	0.981	1.025
	c	0.545	0.590	0.637	0.684	0.731	0.778	0.826	0.875	0.923	0.973	1.024	1.075
1.0	a	1.038	1.075	1.113	1.15	1.188	1.225	1.262	1.300	1.337	1.375	1.412	1.450
	b	1.050	1.100	1.150	1.200	1.250	1.300	1.350	1.400	1.450	1.500	1.550	1.600
	c	1.051	1.103	1.155	1.207	1.261	1.315	1.369	1.422	1.477	1.535	1.592	1.649
1.5	a	1.538	1.575	1.613	1.65	1.688	1.725	1.762	1.800	1.837	1.875	1.912	1.950
	b	1.556	1.613	1.669	1.725	1.781	1.838	1.894	1.95	2.006	2.063	2.119	2.1750
	c	1.558	1.615	1.671	1.728	1.788	1.850	1.913	1.975	2.038	2.000	2.163	2.226
2.0	a	2.038	2.075	2.113	2.15	2.188	2.225	2.262	2.3	2.337	2.375	2.412	2.450
	b	2.063	2.125	2.188	2.251	2.313	2.375	2.438	2.500	2.563	2.625	2.688	2.750
	c	2.066	2.128	2.191	2.255	2.318	2.384	2.448	2.514	2.586	2.657	2.729	2.800
2.5	a	2.538	2.575	2.613	2.65	2.688	2.725	2.762	2.799	2.836	2.873	2.910	2.947
	b	2.569	2.637	2.706	2.775	2.844	2.912	2.980	3.048				
	c	2.571	2.643	2.714	2.786	2.860	2.935	3.010					

rates in women, while Jones and Andersen [20] found that the mean value of beta-slope among females was 0.214 mg/mL/h compared with 0.189 mg/mL/h in males. In our study, no gender differences were established, because the number of investigated women was extremely small (0.5%).

Experimental results of several investigators show that chronic alcohol consumption also affects the elimination rate [3,4,13], i.e. that the rate of ethanol elimination increases with drinking experience. This finding may be the consequence of high individual activity of liver alcohol oxidizing system, or simultaneous distribution and alcohol equivalence between blood and tissue water [11,20].

The results reported in this study are in concordance with results of recent studies using the same methodology. However, these results raise the question of their implications in forensic practice, since they cannot simply be ignored. How big a mistake can a forensic medicine expert make by using standard values of β -slope [8,19,25]? To answer this question, we performed retrograde calculation of BAC_{tc} using three different methods in the interval of $BAC_t = 0.5\text{--}2.5 \text{ g/kg}$, on every 15 min, the time frame of 3 h:

- (a) First, BAC_{tc} was calculated using zero-order model and known formulas for retrograde calculation of BAC_{tc} on the basis of BAC_t found in the blood specimen taken within certain time interval after critical event $BAC_{tc} = BAC_t + (\beta \times t)$, as well as using standard value of elimination factor $\beta_{60} = 0.15 \text{ g/kg}$ (Table 2, row a).
- (b) Consecutively, aforementioned equation has been modified by corrected beta-slope value $\beta_{60} = 0.15 \text{ g/kg} + (0.05 \text{ g/kg} \times \text{BAC})$:

$$BAC_{tc} = BAC_t + [0.15 \text{ g/kg} + (0.05 \text{ g/kg} \times BAC_t)] \times t,$$

followed by calculation according to the same initial values (Table 2, row b).

(c) The main concern of the third applied method was that the time interval needed for the elimination of $\Delta_{\text{BAC}} = 0.1 \text{ g/kg}$ is not always the same, but decreases as the BAC increases. In the first step the beta-slope for BAC_t value has been calculated, followed by the time period (Δ_t) needed for the BAC change of $\Delta_{\text{BAC}} = 0.1 \text{ g/kg}$. The whole procedure has been repeated for the new value of $BAC_t + 0.1 \text{ g/kg}$ within certain time interval (Table 2, row c).

Obtained results have shown that there is a statistically significant difference ($p < 0.05$) in the cases of initially low BAC_t (0.5 g/kg) values, where retrograde calculation ((a) versus (b)) was applied. However, observed relative difference is not high. The difference between methods (b) and (c) is not statistically significant ($p > 0.05$).

In the cases of high BAC_t (2.0 g/kg) values, difference in calculated values of BAC_{tc} obtained by method (a) versus method (b) is statistically significant ($p < 0.01$) and within the first hour could be found at the level of the second decimal point, after which it could be seen at the first decimal point (0.3 g/kg maximal). Difference in calculated BAC_{tc} between methods (b) and (c) is not statistically significant ($p > 0.05$).

5. Conclusion

Results reported in this study demonstrated dependence of β -slope and BAC value. The elimination curve in the BAC interval 0.5–2.5 g/kg has linear trend and for any increase of the BAC value by $\Delta_{\text{BAC}} = 0.1 \text{ g/kg}$ beta-slope increases on average by $\Delta_{\beta_{60}} = 0.005 \text{ g/kg}$.

Reported results show that there is a statistically significant difference between BAC_{tc} values calculated using standard versus corrected method. The higher the BAC_t and the longer the calculation time, the greater and statistically more

significant ($p < 0.01$) is the difference between the calculated values of BAC_{tc} .

Beta-slope correction using time factor (Δ_t) necessary for elimination of $\Delta_{BAC} = 0.1 \text{ g/kg}$ could be neglected, due to the fact that found difference is fairly low (third and second decimal point), and it could not possibly influence forensic and psychiatric expert witness' testimonies, regarding the influence of the established blood alcohol concentration on sensory functions.

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Pharmacokinetics of Ethanol — Issues of Forensic Importance

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Pharmacokinetics of Ethanol — Issues of Forensic Importance

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ABSTRACT: A reliable method for the quantitative analysis of ethanol in microvolumes (50–100 µL) of blood became available in 1922, making it possible to investigate the absorption, distribution, metabolism, and excretion (ADME) of ethanol in healthy volunteers. The basic principles of ethanol pharmacokinetics were established in the 1930s, including the notion of zero-order elimination kinetics from blood and distribution of the absorbed dose into the total body water. The hepatic enzyme alcohol dehydrogenase (ADH) is primarily responsible for the oxidative metabolism of ethanol. This enzyme was purified and characterized in the early 1950s and shown to have a low Michaelis constant (k_m), being about ~0.1 g/L. Liver ADH is therefore saturated with substrate after the first couple of drinks and for all practical purposes the concentration-time (C-T) profiles of ethanol are a good approximation to zero-order kinetics. However, because of dose-dependent saturation kinetics, the entire postabsorptive declining part of the blood-alcohol concentration (BAC) curve looks more like a hockey stick rather than a straight line. A faster rate of ethanol elimination from blood in habituated individuals (alcoholics) is explained by participation of a high k_m microsomal enzyme (CYP2E1), which is inducible after a period of chronic heavy drinking. Owing to the combined influences of genetic and environmental factors, one expects a roughly threefold difference in elimination rates of ethanol from blood (0.1–0.3 g/L/h) between individuals. The volume of distribution (V_d) of ethanol, which depends on a person's age, gender, and proportion of fat to lean body mass, shows a twofold variation between individuals (0.4–0.8 L/kg). This forensic science review traces the development of forensic pharmacokinetics of ethanol from a historical perspective, followed by a discussion of important issues related to the disposition and fate of ethanol in the body, including (a) quantitative evaluation of blood-alcohol curves and the factors influencing the peak concentration in blood (C_{max}) and the time of its occurrence (t_{max}), (b) biological variations in the ADME of ethanol, including the apparent volume of distribution (V_d or rho), the disappearance rate from blood (β or k_0), and the disposal rate by the entire body in 1 h (B_{60}), and (c) questions about ADME of ethanol often arising during the prosecuting of accused drunken drivers.

KEY WORDS: Alcohol, analysis, blood concentration, ethanol, forensic science, legal medicine, pharmacokinetics, toxicology.

INTRODUCTION

Ethanol, commonly referred to as alcohol or grain alcohol (C_2H_5OH), is the psychoactive substance most frequently identified in biological specimens obtained from the living and the dead [115]. Binge drinking and drunkenness are catalysts in many types of criminal activity, including impaired driving, sexual assault, hooliganism, and violence against the person [114,120]. In fact, a recent survey of the relative dangerousness of recreational drugs identified the legal drug ethanol as more of a problem for the individual and society than illicit drugs such as heroin and crack cocaine [200].

The disposition and fate of alcohol and drugs in the body belongs to the scientific discipline known as pharmacokinetics, which is a key subdiscipline of pharmacology and very closely related to pharmacodynamics, which deals with the action of drugs on the body [221]. Reliable information about the absorption, distribution, metabolism, and excretion (ADME) of ethanol is important in forensic science and legal medicine whenever alcohol-related crimes, such as drunken driving or drug-related sexual assault, are investigated [138]. An expert witness might be asked to estimate a person's blood-alcohol concentration (BAC) based on information about the

number of drinks consumed or to calculate the amount of alcohol in the body from the measured BAC [58].

The relationship between BAC and impairment of body functioning, and a person's ability to form specific intent after drinking alcohol, are examples of other questions that require knowledge about the pharmacology and the ADME of ethanol [135]. Experiments on the pharmacokinetics of ethanol have enabled the estimation of a driver's BAC at the time of driving based on that person's BAC obtained at the time of sampling blood, which is often several hours later [3,193]. Such a calculation is often referred to as retrograde extrapolation or backtracking, and this requires making certain assumptions about the ADME of ethanol [157,158].

This forensic science review deals with the disposition and fate of ethanol in the body and traces the development of forensic pharmacokinetics from a historical perspective. The quantitative evaluation of blood-alcohol curves is described along with the factors influencing the peak concentration in blood (C_{max}) and the time of its occurrence (t_{max}). Biological variations in the ADME of ethanol, including the apparent volume of distribution (V_d or rho), the disappearance rate from blood (β or k_0), and the disposal rate by the entire body in 1 h (B_{60}), are documented and explained.

Historical Background

The word pharmacokinetics was obtained by combining two Greek words: “*pharmakon*,” meaning a drug or poison, and “*kinesis*,” which means movement [248]. Pharmacokinetics is therefore concerned with the quantitative evaluation of concentration-time (C-T) profiles of drugs in blood, plasma, urine, or saliva after a specified route of administration (e.g., orally, intravenously, rectally, or subcutaneously).

The first appearance in print of the word pharmacokinetics was in 1953 in Friedrich H. Dost’s book *Der Blutspiegel — Kinetik der Konzentrationsabläufe in der Kreislaufflüssigkeit*, on page 244 [51]. An English translation of the book title is *The Blood-profile — on the Kinetics of Concentration Changes in the Systemic Circulation*. In this book, Dost derived mathematical formulas appropriate to describe the C-T profiles of endogenous and exogenous substances in blood or plasma after intra- and extravascular routes of administration [52].

Erik M.P. Widmark

Knowledge about forensic pharmacokinetics of ethanol owes much to the pioneering research and publications of Erik M.P. Widmark (1889–1945), a professor of physiological chemistry at the University of Lund in Southern Sweden [97]. In 1922 Widmark introduced a microdiffusion method for the quantitative analysis of ethanol in blood, which was a prerequisite for later studies of the ADME of ethanol [262]. His dual qualifications in science and medicine and good grounding in mathematics put Widmark in a strong position to make original contributions to knowledge about the pharmacokinetics of ethanol as well as other substances, such as acetone and methanol.

The microdiffusion method of blood-alcohol analysis was fully validated and subsequently used in several European countries as a way to furnish evidence for prosecution of drunken drivers depending on the measured BAC [103]. Statutory blood-alcohol limits for driving were introduced in Sweden in 1941 (0.8 mg/g or ~0.08 g%) and in Norway in 1936 (0.5 mg/g or ~0.05 g%) [104]. However, it was not easy for a judge and jury to interpret the meaning of a person’s BAC in relation to the amount of alcohol consumed. So the BAC was reported along with information about the number of centilitres of spirits (40% v/v) in the body at the time the blood sample was taken. The general public also wanted information about the number of drinks they might consume before exceeding the statutory BAC limit for driving. This required controlled alcohol-dosing studies in men and women of different ages, body weights, and body compositions to determine the ADME of ethanol.

Table 1 presents a timeline of historical events leading to the development of pharmacokinetics, with major focus on ethanol and the contributions made by pioneer workers in this field.

Widmark Parameters

Widmark’s seminal work on the subject of ethanol pharmacokinetics appeared in a 1932 German publication, *Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung* [261]. This is considered a veritable classic of the alcohol literature, as evidenced by its republication in English in 1981 under the title *Principles and Applications of Medicolegal Alcohol Determination* [263].

This monograph contained 12 chapters dealing with, among other things, the analysis and disposition of ethanol, methanol, and acetone in body fluids, the pharmacokinetic profiles of these substances, the relationship between a person’s BAC and the signs and symptoms of drunkenness, the relationship between BAC and the quantity of alcohol consumed, as well as aspects of alcohol analysis and interpretation in cadavers [263].

The BAC profiles determined in controlled drinking studies were used to develop the concepts of zero-order elimination from blood (β), volume of distribution (rho), and rate of disposal of ethanol from the entire body. The rho factor, perhaps better known today as the volume of distribution or V_d , was smaller in women 0.55 (range 0.49–0.76) than in men 0.68 (range 0.51–0.85). This gender difference was statistically highly significant ($p < 0.001$) and depended on the fact that the female body had a smaller amount of water per kilogram of body weight than the male body, thus a smaller volume was available to dilute the ingested ethanol [220].

The other important pharmacokinetic parameter was the rate of elimination of ethanol from the bloodstream; experiments with 20 men and 10 women gave average values of 0.15 mg/g/h (SD 0.0336) in men and 0.156 mg/g/h (SD 0.0222) in women [261]. This small gender difference was not considered statistically significant ($p > 0.05$), although a closer examination of the results, as well as many later studies by others, showed that the slope of the declining phase of the BAC curve was slightly steeper in women compared with men [23,45].

The importance attached to the values of β and rho in various blood-alcohol calculations necessitated making further drinking studies, and by the early 1940s pharmacokinetic parameters of ethanol were available for 30 men and 30 women [203]. The mean distribution volumes (V_d) of ethanol was now considered ~0.70 for men and ~0.60 for women and the elimination rate from blood was 0.15

Table 1. Timeline in the development of knowledge about the subject of pharmacokinetics with special reference to ethanol pharmacokinetics and tributes to the pioneer workers involved

Year	Scientist ^a	Contribution to pharmacokinetics of alcohol
1874	Francis Anstie (1833–1874)	British physician; much concerned with public health in Victorian England and especially the problem caused by overconsumption of alcohol. He established the so-called “Anstie limit”, a recommended daily dose of alcohol (1.5 oz of 100% ethanol), corresponding to ~100 mL of 40% v/v liquor [11]. He developed a method for quantitative analysis of ethanol in body fluids by oxidation with a mixture of potassium dichromate and sulfuric acid. Using this method, Anstie demonstrated that only a very small fraction of the alcohol a person consumed was eliminated from the body unchanged in breath and urine [7]. Moreover, he wrote one of the first books on the subject of “Stimulants and Narcotics”.
1919	Edward Mellanby (1884–1955)	British physician and pharmacologist; investigated factors influencing shapes of blood-alcohol curves after drinking. Experimenting with humans and animals (dogs), Mellanby showed the importance of administered dose and the type of beverage (beer and stout vs spirits), as well as the influence of food and milk in the stomach before drinking [187]. Mellanby was the first to suggest a constant rate of alcohol elimination from blood, hence zero-order kinetics. Mellanby also studied impairment effects of alcohol, showing that these were more pronounced on the rising phase compared with the declining phase of the BAC curve. This phenomenon, known as acute tolerance, occurs during a single exposure to ethanol and was later referred to as the “Mellanby effect” [186].
1932	Erik M.P. Widmark (1889–1945)	Professor of physiological chemistry at the University of Lund in Sweden [6]; Widmark published seminal articles on the disposition and fate of acetone, ethanol and methanol in the body during the first half of the 20th century. His micro-diffusion method of blood-alcohol analysis was highly reliable and became used for legal purposes in some nations [262]. The pharmacokinetics of ethanol were studied in men and women and the parameters β and ρ were derived [261]. Beta represents the rate of elimination of alcohol from the bloodstream and ρ is the distribution of alcohol between the entire body and the blood. Widmark’s German monograph from 1932 is a veritable classic of the forensic alcohol literature.
1937	Torsten Teorell (1905–1992)	Professor of physiology and medical biophysics at the University of Uppsala in Sweden; Teorell published two papers in 1937 that later became widely acclaimed as pioneer contributions to knowledge about compartment models and pharmacokinetics of drugs given by intra- and extra-vascular routes of administration [243,244]. For this contribution, Teorell is considered one of the founding fathers of pharmacokinetic theory, although he never concerned himself with the pharmacokinetics of ethanol. The speed of distribution of drugs into the body fluids and tissues was discussed in relation to the route of administration and the concept of compartment models was formulated.
1951	Antti Alha (1917–1989)	Physician and forensic toxicologist from Helsinki, Finland; made extensive studies of the human pharmacokinetics of ethanol. Alha made use of the methods developed by Widmark to evaluate blood-alcohol curves from a large number of controlled drinking studies with male subjects. Four different doses of alcohol were administered and the pharmacokinetic parameters were derived from individual curves as a function of dose. Also investigated were quantitative aspects of drunkenness thus establishing clinical signs and symptoms in relation to the individual’s BAC [4]. The results of this work appeared in a monograph (92 pp) in English that was not very widely circulated. Nevertheless, this was a classic study of blood-alcohol curves and forensic pharmacokinetics of ethanol.
1953	Friedrich H. Dost (1910–1985)	Physician and professor of pediatrics at the University of Giessen in Germany; Dost is considered a pioneer of clinical pharmacokinetics and is credited with coining the word in 1953, which first appeared in print in his famous book “Der Blutspiegel” [51]. This presented a review of all the literature on the subject of pharmacokinetics of drugs; mathematical formulas and equations were derived to describe blood- and plasma- concentration-time profiles of endogenous and exogenous substances.
1969	John G. Wagner (1921–1998)	Professor of pharmaceutics at the College of Pharmacy at the University of Michigan, U.S. Wagner wrote several books on the subject of biopharmacy and pharmacokinetics and was a strong proponent for use of the Michaelis-Menten equation or saturation kinetics to describe the C-T profiles of ethanol [251,253]. Wagner and his collaborators published several articles on the pharmacokinetics of ethanol including the effect of dose, eating solid or liquid meals [168,227], and oral vs intravenous administration in the fasting state [267–269]. Wagner verified that the area under the blood-alcohol curve increased more than proportionally with increasing dose, which is characteristic of drugs metabolized by non-linear kinetics.

^a Photos were scanned from the author's own archive.

mg/g/h, being independent of gender. In these first pharmacokinetic studies, the BAC and C_0 were reported in the concentration unit of mg/g or g/kg so the rho factor, which is the ratio of dose (g/kg)/ C_0 (mg/g) has no dimensions, whereas today, because BAC is mostly in mass/volume (g/L), the rho factor has units of L/kg.

Some investigators failed to confirm the values of β and rho reported by Widmark, although this often depended on some departure from the experimental design, namely the need to administer a bolus dose of ethanol as neat spirits on an empty stomach. Others failed to appreciate that BAC was in mass/mass concentration units (mg/g or g/kg), which influences the values of β and rho (see *Blood- and Breath-Alcohol Concentration Units* below). Eating a meal before drinking, even a sandwich or snack, lowers the bioavailability of the dose of ethanol, and the distribution factor (rho or V_d) as calculated from the ratio dose/ C_0 tends to be abnormally high under these conditions.

Ethanol pharmacokinetics and the various factors influencing ADME of this legal drug have been the subject of many previous review articles and some of these are worthy of note [85,86,136,198,255,265].

Physicochemical Properties of Ethanol

Ethanol is a small polar molecule that mixes with water in all proportions and distributes into the total body water space. Unlike many other drugs, there is no evidence that ethanol binds to plasma proteins and its solubility in lipids is insignificant compared with solubility in water. These special properties of ethanol require that large quantities need to be consumed to raise the BAC to elicit pharmacological effects. Mild euphoria from ethanol is usually achieved after rapid drinking of about 20 g (20,000 mg). This compares with 10 mg morphine, 10 mg diazepam, 100 mg codeine, or 1,000 mg aspirin to obtain a desired therapeutic effect from these common medications. The main physicochemical properties of ethanol are presented in **Table 2**.

Blood- and Breath-Alcohol Concentration Units

The standard operating procedure with the microdiffusion method of blood-alcohol analysis required that the aliquots of whole blood (~100 mg) were weighed on a torsion balance, so the final analytical result was reported in units of mass/mass, actually mg/g or g/kg. With more modern analytical methods, such as gas chromatography, the aliquots of blood are measured by volume and the BAC is reported in units of mass/volume, such as g/100 mL (U.S.), mg/100 mL (U.K.) or g/L and mg/mL (Europe). The connection between mass/mass and mass/volume is the density of whole blood, which on the average is 1.055 g/mL, making a difference of 5.5%

Table 2. Summary of the physicochemical properties of ethanol

Property	Accepted value
CAS number ^a	64-17-5
Molecular weight	46.07 g/mol
Empirical formula	C_2H_6O
Molecular formula	CH_3CH_2OH (primary aliphatic alcohol)
Structural formula	<pre> H H H - C - OH H H </pre>
Common name	Beverage or grain alcohol
Manufacture	Fermentation of starch, sugar or some other source of carbohydrate
Solubility in water	Mixes completely in all proportions
Boiling point	78.5 °C at atmospheric pressure
Melting point	-114.1 °C
Density	0.789 g/mL at 20 °C
pK _a	15.9 at 25 °C
Dipole moment (polarity)	1.69 D
Dielectric constant (polarity)	24.3

^a Chemical Abstract Service registry number.

between mass/mass and mass/volume units [150]. This must be considered when the pharmacokinetic parameters of ethanol (β and rho) are compared and contrasted between studies, because the values depend on whether the C-T profiles were plotted based on mass/mass or mass/volume units (**Table 3**).

The statutory BAC limits for driving in the Nordic countries and in Germany are defined as per mille (parts per thousand) and this refers to mass/mass units, whereas most other nations report BAC as mass/volume [103]. Punishable limits of breath-alcohol concentration (BrAC) were introduced much later than statutory blood-alcohol limits; ethanol was determined in a known volume of exhaled air (mass/volume) and statutory BrAC limits were reported as mg/L, g/210 L, or µg/L depending on the particular country (**Table 4**).

I. ALCOHOL IN THE BODY

The disposition and fate of ethanol in the body is usually illustrated by plotting the concentrations in blood or plasma as a function of sampling time after the start of drinking. Hundreds of controlled drinking experiments with healthy men and women have been done over the years with ethanol taken in the form of beer, wine, or

Table 3. The effect on Widmark's factors (β and rho) when blood-alcohol concentration (BAC) is measured in mass/mass or mass/volume concentration units (density of whole blood was taken as 1.055 g/mL) [261]

Pharmacokinetic parameter	BAC (mass/mass) ^a		BAC (mass/volume) ^a	
	Men (n = 20)	Women (n = 10)	Men (n = 20)	Women (n = 10)
β -slope	0.150 ± 0.0336	0.156 ± 0.0222	0.158 ± 0.0354	0.164 ± 0.0234
Rho factor (V_d)	0.68 ± 0.085	0.55 ± 0.055	0.64 ± 0.081	0.52 ± 0.0521

^a Values shown are “mean ± SD”.

Table 4. Concentration units used by various countries to report blood-alcohol concentration (BAC) and breath-alcohol concentration (BrAC) for legal purposes

Conc. unit	Country where used
<i>BAC unit</i>	
mg/g (g/kg)	Denmark, Finland, Germany, Norway, Sweden
mg/mL (g/L)	Austria, Belgium, France, Holland, Spain
mg/100 ml (mg/dL)	Canada, Ireland, New Zealand, U.K.
g/100 mL (g%)	Australia, U.S.
<i>BrAC unit</i>	
mg/L	Austria, Denmark, Finland, Germany, Norway, Sweden, Spain, and some other EU countries
μg/L	Holland, New Zealand
μg/100 mL	Ireland, U.K.
g/210 L	U.S.

spirits either on an empty stomach or after subjects had eaten a meal. The shapes of BAC curves derived in this way have formed the basis of our current knowledge about the human pharmacokinetics of ethanol.

Figure 1 shows a BAC profile for one healthy male subject who drank ethanol (0.68 g/kg) as neat whisky on an empty stomach (overnight fast). Also shown is the best-fitting straight line (dashed) to selected C-T data points on the postabsorptive portion of the BAC curve. Extrapolating this line to intersect the y- and x-axes gives two important pharmacokinetic parameters, namely the y-intercept (C_0) and the x-intercept (min_0). These empirical values are used to calculate the elimination rate of ethanol from blood (β) and the distribution volume (rho), as shown within the text boxes in the figure. Alternatively, the values of C_0 and β are obtained by least-squares linear regression analysis using selected C-T points on the postabsorptive declining phase of the BAC.

C-T curves of ethanol show several common features beginning with an increase in BAC immediately after the start of drinking, which reflects the absorption of ethanol

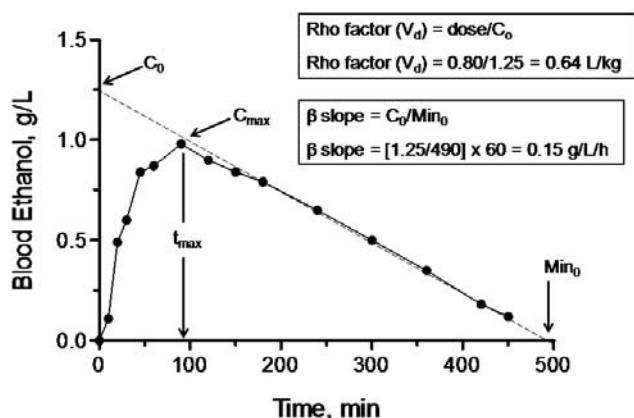


Figure 1. A typical blood-alcohol curve in one male subject who ingested 0.68 g ethanol per kg body weight as neat whisky on an empty stomach. Samples of capillary (fingertip) blood were taken for analysis of ethanol at repeated intervals and pharmacokinetic parameters β and rho were derived as shown in the text boxes. (Revised version of a figure appearing in the author's earlier publications [97,104].)

from the stomach and intestine into the bloodstream. The absorption, distribution, and elimination processes occur simultaneously but at different rates. When drinking ends and more and more ethanol passes from the gut into the blood, the rate of absorption slows and eventually becomes equal to the rate of removal of ethanol from the bloodstream by metabolism and excretion processes. This marks the starting point of the postabsorptive phase and provided no more alcohol is consumed, the BAC then decreases at a constant rate per unit time until reaching a fairly low BAC of 0.1–0.2 g/L.

The shapes of BAC curves show considerable interindividual variations even under standardized drinking conditions; that is to say, when the same dose (gram per kilogram of body weight) is ingested as the same type of beverage in the same space of time. These variations are seen in **Figure 2**, which shows BAC curves for nine male subjects after they drank neat whisky on an empty stomach. Most of the intersubject variation is seen during the first 120 min after start of drinking, which corresponds to the absorption phase.

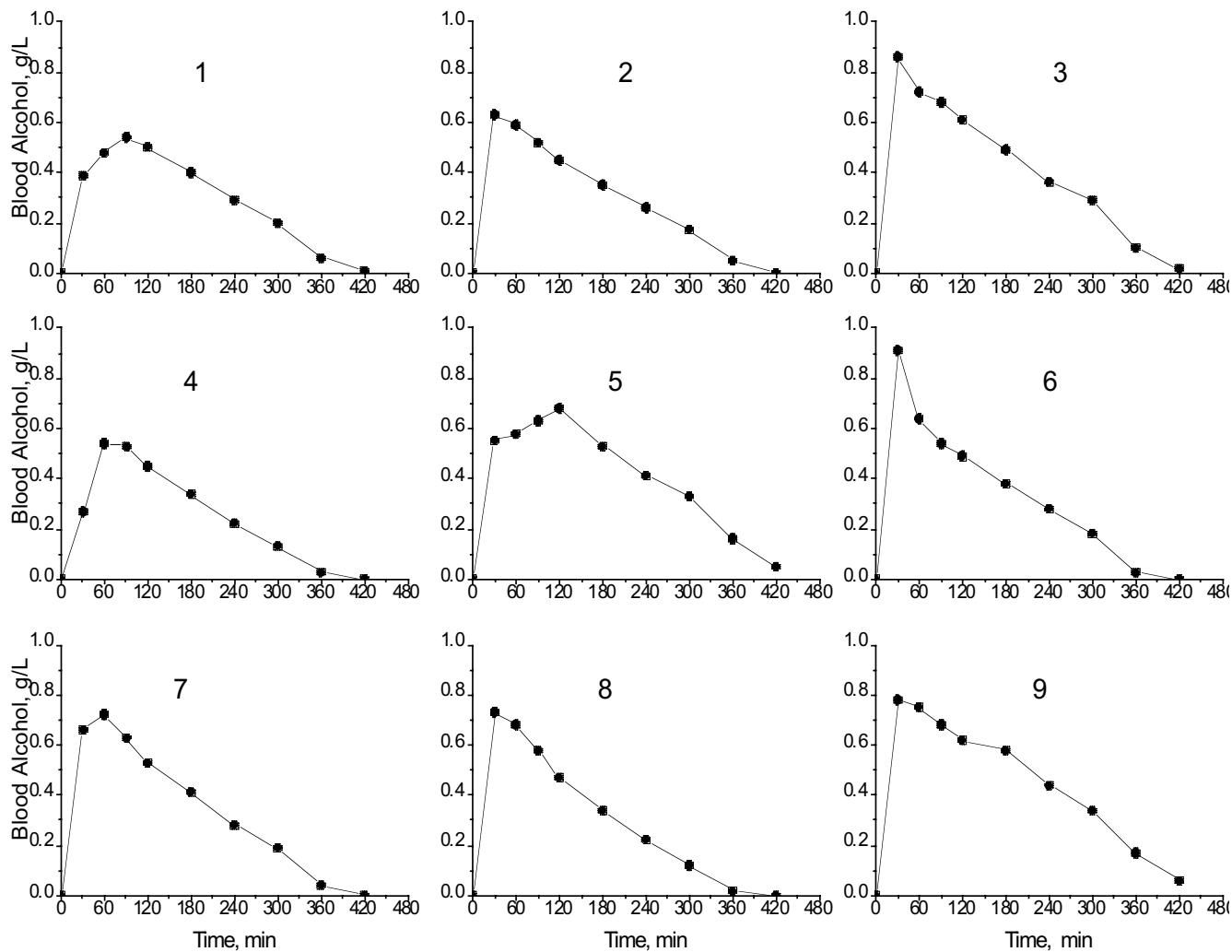


Figure 2. Examples of blood-alcohol profiles obtained in drinking experiments with nine healthy men after they drank ethanol (0.68 g per kg body weight) as neat whisky on an empty stomach. (Simplified version of a figure appearing in the author's earlier publication [102].)

The time-course of a drug in the body is usually discussed in terms of its absorption, distribution, metabolism, and excretion (ADME), and one aim of pharmacokinetics is to describe these processes in quantitative terms. **Table 5** illustrates graphically the ADME processes for a drug such as ethanol.

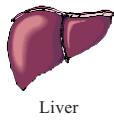
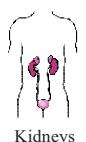
A. Absorption

Absorption is the process by which a drug or poison passes from the site of administration into the bloodstream for distribution throughout all body fluids and tissues. Small amounts of alcohol can enter the blood by absorption through the mucous surfaces of the oral cavity, especially if a drink is held in the mouth for a sufficiently long time without swallowing. But for all practical purposes alcoholic drinks are swallowed and absorption from the gastro-intestinal canal occurs by a passive diffu-

sion across the gut lumen, at rates that depend on the prevailing concentration gradient in accordance with Fick's law [15].

Because ethanol is already in liquid form, dissolution or solubilization is not necessary for absorption to occur, which means that the absorption time lag is negligible and ethanol is measurable in the blood immediately after drinking starts. The absorption of drugs taken in the form of tablets first requires dissolution and the speed and extent of absorption depends on properties of the parent drug, such as its pKa and lipid solubility. This leads to a measurable lag-time before the active substance is detectable in the venous blood circulation. The absorption of ethanol is faster from the upper part of the intestines (proximal small bowel), owing to the larger absorption surface area provided by the villi and microvilli of the duodenum and jejunum.

Table 5. Organ systems involved in the absorption, distribution, metabolism, and excretion of ethanol, and comments about these processes

Stage	Organ system involved ^a	Comments about the process
Absorption	 Stomach  Intestines (gut)	Absorption of ingested ethanol starts already in the stomach through the mucous surfaces of the lumen. The rate of uptake into the blood occurs much faster from the duodenum and small intestine, owing to the much larger surface area provided by the villi and microvilli. Gastric emptying is a major determinant of the speed of ethanol absorption and has a major influence on the C_{max} and t_{max} of blood-alcohol curves.
Distribution	 Arterial/venous blood circulation	After absorption from the gastrointestinal tract, ethanol is transported throughout all body organs and tissues with the blood circulation. Ethanol passes freely across biological membranes and distributes into the total body water space without binding to plasma proteins. However, a concentration gradient exists between the concentrations in arterial (A) and venous (V) blood; with A > V during absorption and V > A during the postabsorptive period.
Metabolism	 Liver	Ethanol reaches the liver mixed with the portal venous blood where oxidative enzymes, e.g., alcohol dehydrogenase (ADH), start to remove ethanol from the bloodstream. The ADH enzyme has a low k_m and is therefore saturated with substrate after the first couple of drinks. For most forensic purposes, the elimination rate of ethanol from blood is constant per unit time in accordance with zero-order kinetics.
Excretion	 Lungs  Kidneys	Only a small fraction (2–10%) of the total dose of ingested ethanol is eliminated from the body unchanged via the lungs (breath) and kidneys (urine), and trace amounts in sweat. Excretion is a first-order process and proportionally more of the dose of ethanol gets eliminated unchanged after increasing amounts are consumed and higher BACs are reached. Drinking massive amounts of water to cause diuresis or hyperventilation are not very effective ways to increase the rate of ethanol clearance from the body.

^a Organ systems are clip art in the public domain.

1. Drinking Pattern and Dosage Form

The pattern of drinking (bolus or repetitive drinking), the concentration of ethanol in the drink, and the presence of food in the stomach are major determinants of the speed of ethanol absorption into the blood. The time elapsed after the start of drinking before C_{max} is reached, which is denoted as t_{max} and the ratio of C_{max} to t_{max} is a crude index of the rate of absorption of ethanol (g/L/h). Based on a large number of drinking studies, t_{max} usually occurs within 60 min after the end of drinking, although in any individual case this time might range from 5 min to 120 min depending on many factors.

An example of a BAC curve showing very rapid absorption of ethanol is shown in Figure 2 (subject 6), where an overshoot peak is evident and C_{max} is higher than expected for the dose of ethanol administered. The C_{max} is immediately followed by a diffusion plunge and during this time the excess ethanol in the blood reequilibrates between the vascular system and the rest of the body water, a process that takes ~30–45 min. Another curve in Figure 2 (e.g., subject 5) shows an initial swift absorption with a marked rise in BAC, although this is followed by a much slower increase before reaching C_{max} . Under some circumstances the BAC profile shows no obvious C_{max} and instead a plateau develops, during which time the BAC remains more or less unchanged for

60–120 min before the rectilinear declining phase begins. Note that ethanol is still being metabolized even when the BAC remains unchanged for several hours.

The dosage form of ethanol corresponds to the nature of the drink consumed, whether whisky, gin, vodka, wine, beer, or even 95% v/v ethanol diluted with water [75]. In a German study, BAC curves were not much different when 0.75 g/kg ethanol was consumed on an empty stomach as 4%, 8%, 20%, and 44% v/v dilutions with water [236]. This suggests that the volume of fluid in which ethanol is taken is less important for determining C_{max} and t_{max} provided the dose of ethanol remains the same. This seems to conflict with the notion of absorption being a passive diffusion process according to a concentration gradient, which emphasizes the role of other factors, such as efficacy of gastric emptying. Besides different concentrations of ethanol, alcoholic beverages differ in composition, such as the amount of carbohydrates and other constituents they contain, which also influences the rate of ethanol absorption into the blood by influencing gastric emptying [273].

2. Gastric Emptying

The single most important factor controlling the speed of absorption of ethanol into the bloodstream is the emptying rate of the stomach, which is controlled by the

pyloric sphincter. The pylorus is normally almost totally closed, owing to tonic contraction of the pyloric muscle. Factors influencing stomach emptying and the pylorus valve are of paramount importance for how fast alcohol is absorbed into the blood and the values of C_{\max} and t_{\max} of the resulting BAC curve.

3. Effects of Food

The presence of food in the stomach before drinking has a major influence on both rate and extent of absorption of ethanol as shown already by experiments done in the 1930s [264]. The composition of the food in terms of macronutrients (carbohydrate, protein, or fat) seemed less important in delaying the rate of absorption of ethanol than the amount (bulk) of food eaten before drinking [125].

Figure 3 shows BAC profiles obtained in a cross-over design experiment when four individuals drank the same dose of ethanol (0.80 g/kg) under fed or fasting conditions [117]. Without exception, the curves in the fed state ran on a lower level compared with the curves when alcohol was taken on an empty stomach. This gave the impression that a smaller amount of alcohol had been administered after the meal, but this was not the case. The C_{\max} was appreciably lower, the t_{\max} occurred later, and AUC was reduced when subjects had eaten a standardized breakfast before drinking. Moreover, in the fed state the BAC curves returned to zero about 1–2 h earlier, which suggests an overall faster rate of metabolism. Because the slopes of the rectilinear declining portions were not much different in the fed and fasting conditions, it seems that the

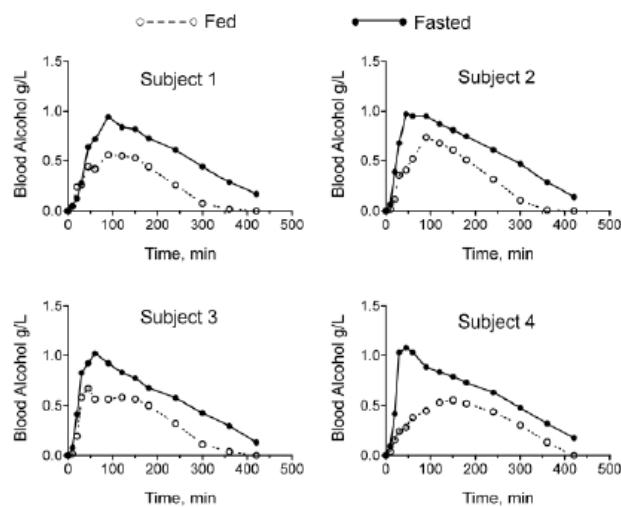


Figure 3. Within-subject experimental design showing food-induced lowering of blood-alcohol profiles in four healthy men after they drank ethanol (0.80 g/kg) as vodka diluted with orange juice after an overnight fast or immediately after eating a standardized breakfast. (Simplified version of a figure appearing in the author's earlier publication [117].)

accelerating effect of food on ethanol metabolism occurs during the absorption phase.

When small amounts of ethanol (e.g., 0.3 g/kg) were consumed after a meal, the resulting BAC curves were highly variable, as shown in **Figure 4**. Although C_{\max} , t_{\max} , and AUC can be read from the BAC curves, it is not practical to make pharmacokinetic analysis and curve fitting of C-T points on the postabsorptive phase. The BAC curves in Figure 4 were obtained in experiments involving 10 men who drank ethanol diluted with orange juice 15 min after they had eaten a standardized breakfast.

Other factors influencing gastric emptying include some prescription drugs, anatomy of the gut, smoking cigarettes, surgical operations (gastric bypass), stress, and trauma, as summarized in **Table 6**.

4. Rectal Administration

The speed and completeness of absorption of a drug depends on the route of administration, whether by mouth (orally), intravenously (parenterally), by inhalation via the lungs, through the skin (transdermally), or rectally. Alcohol is not absorbed through the intact skin in any mea-

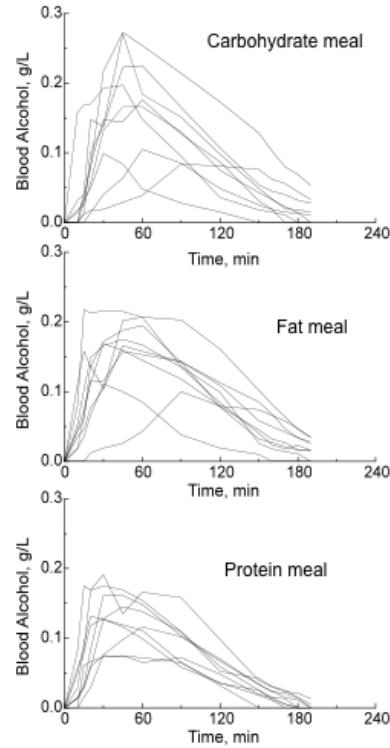


Figure 4. Highly variable blood-alcohol curves for nine subjects who drank the same small dose of ethanol (0.30 g/kg) in 15 min after eating fat-rich, carbohydrate-rich, or protein-rich meals. (Revised versions of figures appearing in the author's earlier publications [118,198].)

Table 6. Examples of the many factors that might result in a slow or fast absorption of alcohol by influencing gastric emptying

Slow rate	Fast rate
Using medication that delays gastric emptying, e.g., anticholinergic agents, propantheline [54]	Drugs that accelerate gastric emptying (e.g., cisapride, metoclopramide, erythromycin)
Beer with a high carbohydrate content compared with alcohol as neat spirits	Rapid ingestion of neat spirits as opposed to sherry, table wine, or beer
Pyloric spasm caused by irritation of gastric mucosa by ethanol in neat spirits	Drinking on an empty stomach, except if a pyloric spasm occurs [102]
Eating a meal before drinking alcohol [222,256]	Highly carbonated (CO_2) drinks or with various sweeteners [274]
Trauma, shock and massive blood loss	Low blood-sugar content (hypoglycemia)
Smoking cigarettes [92]	Surgery to the gut, gastric bypass or gastrectomy [139,272]

surable amount, as demonstrated in two recent studies that confirmed results from older work [19,82,225]. Ethanol can be given as an enema via the rectum as exemplified by the C-T profiles in **Figure 5** depicting two individuals denoted A and B [166]. These curves were obtained when 45 g of ethanol was diluted to 300 mL with water and administered per rectum in the course of 35–40 min.

5. Pulmonary Inhalation

Absorption of alcohol into the bloodstream by inhalation via the lungs is not an effective way to raise the BAC for several good reasons. First, the ethanol contained in the inhaled air gets dissolved in the mucous surfaces covering the upper airway and leaves the lungs again with the next exhalation [28,141,183]. Second, very high concentrations of ethanol in the ambient air breathed are necessary and such concentrations are not tolerated by humans [151]. Third, the amount of ethanol absorbed into the bloodstream via the lungs must exceed the hourly rate of ethanol metabolism, which is about 7–8 g/h. This makes it practically impossible for BAC ($> 0.1 \text{ g/L}$) to increase by breathing ethanol contained in the ambient air.

If a person has an elevated BAC before entering a closed room or chamber containing ethanol vapors in the air breathed, then under these conditions, especially with high respiratory minute volumes — e.g., after strenuous exercise — the amounts of alcohol absorbed into pulmonary blood by inhalation might balance the amount lost by metabolism. If the blood-alcohol curve is in the postabsorptive declining phase when inhalation of ethanol vapor begins, the slope of the declining phase on the BAC curve is decreased considerably [141].

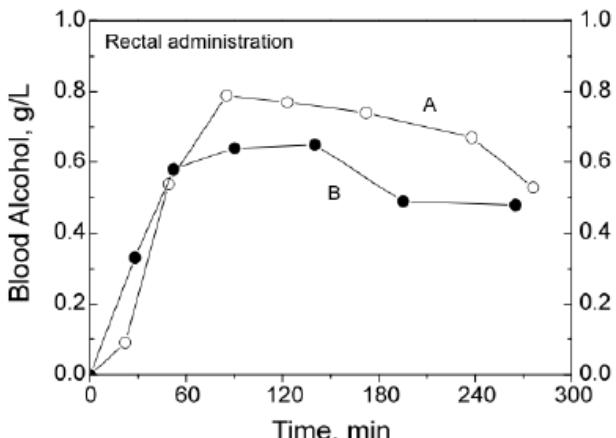


Figure 5. Blood-alcohol curves in two subjects (A and B) when the dose of alcohol was administered rectally. (Figure is constructed based on data appearing in Ref. [166].)

6. Absorption Kinetics

The absorption of ethanol into the blood is highly variable even when drinking occurs on an empty stomach. The peak BAC might occur 5–10 min after end of drinking (Figure 2 curves 3, 6, 8, and 9) or as late as 120 min (curve 5) and such slow absorption, despite drinking neat spirits on an empty stomach, is probably explained by an ethanol-induced pyloric spasm.

The absorption of ethanol into the blood after oral ingestion is often considered a simple first-order process, but this is an oversimplification because of the variable and unpredictable nature of gastric emptying. The speed of absorption as reflected in the rate constant (min^{-1} or h^{-1}) is slower from the stomach (longer half-life) compared with the small intestine (shorter half-life), which makes it difficult to fit a pharmacokinetic model to the entire absorption process. In forensic science situations, great care is needed when a statement is made about the absorption rate constant for ethanol for any given drinking scenario.

The BAC curve shown in **Figure 6** was obtained in a 23-year-old male subject who drank 0.68 g/kg ethanol as neat whisky on an empty stomach resulting in a C_{\max} at 100 min after the end of drinking. The C-T data points on the rising phase of the curve (**Table 7**) can be used to determine the absorption rate constant assuming first-order kinetics by the graphic method of residuals.

The residuals method requires subtracting the BACs determined during absorption phase from BACs at the same time points read from the dashed line extrapolated back to intersect the y-axis corresponding to the time of starting to drink (C_0). This gives a series of residual BACs, which on transformation to natural logarithms and plotted against sampling time (see insert graph in Figure 6) results in a straight line and least squares linear regres-

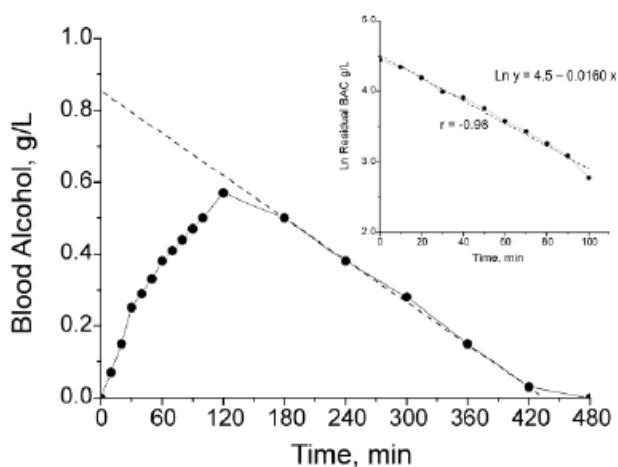


Figure 6. Blood-alcohol curve in one male subject after ethanol (0.68 g/kg) as neat whisky and when absorption into the blood was relatively slow. The method of residuals was used to determine the first-order absorption rate constant. (Figure is constructed based on data collected in the author's laboratory.)

sion analysis of \ln residual BAC (y) and time (x) gives the equation $y = 4.5 - 0.0160 x$ ($r = 0.98$). The regression coefficient is the first-order absorption rate constant ($k_{abs} = -0.0160 \text{ min}^{-1}$), which corresponds to an absorption half-life of 43.3 min ($t_{1/2} = 0.693/k_{abs}$), indicating a slow rate of ethanol absorption for this individual, probably caused by a pyloric spasm after drinking neat whisky.

Experience from evaluating hundreds of BAC curves verifies the difficulty in determining a first-order absorption rate constant, especially when neat spirits are consumed on an empty stomach. Under these conditions the peak BAC often occurs 10 min after end of drinking and residual method is not applicable because of a lack of data points [102]. Instead, a more pragmatic approach is to

divide C_{max} with t_{max} to give a rate of absorption as g/L/h. Moreover, in the real world people drink alcohol intermittently, sometimes over several hours as different types of drinks with or without food, and the BAC increases gradually for each additional drink taken. With this pattern of drinking, much of the total dose of alcohol is already absorbed into the blood during the drinking period and the peak BAC is reached shortly after finishing the last drink.

B. Distribution

After absorption from the stomach and intestines, ethanol enters the portal venous blood and gets transported first to the liver, then to the right side of the heart, and via the lungs, back to the heart and throughout the entire systemic circulation. The rate of equilibration of ethanol between the water fraction of the blood and the extracellular fluids and tissue depends on the cross-sectional area of the local capillary bed and blood flow per gram of tissue. Organs with a rich blood supply, such as the brain and kidney, equilibrate rapidly with ethanol in the blood, whereas bulky skeletal muscle with a lower ratio of blood flow to tissue mass equilibrates more slowly.

1. Total Body Water

Ethanol distributes into total body water and the concentrations at equilibrium in the various body fluids and tissues depend primarily on their relative water contents. This means that sweat, saliva, cerebrospinal fluid (CSF), and urine, which are almost 100% water, have a higher concentration of ethanol than the blood, which is 80% w/w water [26,100,101,185]. Likewise, the concentrations of ethanol in plasma and serum, which contain ~92% w/w water, are higher than an equal volume of whole blood. The plasma/blood distribution ratio averages about 1.15 with a 95% range from 1.10–1.20 [29,270].

2. Gender Differences

From 50–60% of a person's body weight is water, which on the average is higher in men than in women, because of gender differences in lipid (fat) content per kilogram of body weight [55,71,110]. The volume of blood is about 70–80 mL/kg body weight independent of gender, which corresponds to 4.9–5.6 L in a person weighing 70 kg. For a water-soluble drug like ethanol, the volume of distribution corresponds very closely with the total body water (TBW) as verified by isotope dilution experiments using $^2\text{H}_2\text{O}$, $^3\text{H}_2\text{O}$, and H_2O^{16} as tracers [57,199].

The larger the individual in terms of height and body weight, the more body water space available for dilution of the ingested alcohol. For this reason, in experimental

Table 7. Blood-alcohol concentrations during the absorption phase used to calculate a first-order absorption rate constant by the method of residuals (see inset graph in Figure 6)

Time (min)	Actual BAC ^a	Extrapolated BAC ^a	Residual BAC ^a	Ln Residual BAC ^a
0	0	86	86	4.45
10	7	84	77	4.34
20	15	81	66	4.19
30	25	79	54	3.99
40	28	78	50	3.91
50	33	76	43	3.76
60	38	74	36	3.58
70	41	72	31	3.43
80	44	70	26	3.26
90	46	68	22	3.09
100	50	66	16	2.77

^a BACs reported here in units of mg/100 mL to avoid negative logarithms.

alcohol research the dose of ethanol is almost always administered per kilogram of body weight or per kilogram of body water, which permits direct comparisons between different individuals with varying body weights.

Gender difference in TBW is the main reason that women reach a higher BAC than men for the same dose of alcohol administered per kilogram of body weight. Differences in TBW are reflected in gender-related differences in volume of distribution, which averages 0.6 L/Kg for women and 0.7 L/Kg for men [142,177,196]. The V_d for ethanol depends on the ratio of water in the body to water in the blood (80% w/w), and this should be considered when ethanol-dilution experiments are used to determine TBW [172,257]. If the pharmacokinetics of ethanol had been determined from analysis of plasma or serum, which contain ~15% more ethanol than an equal volume of whole blood, a higher y-intercept (C_0) would mean lower V_d derived as dose/ C_0 [113].

Several studies have looked specifically at blood-alcohol pharmacokinetics in women in relation to their age and body composition to complement the results from early studies by Widmark and others [43,196].

3. Body Mass Index and Obesity

Body mass index (BMI) is the ratio of a person's weight in kilograms to the square of height in meters and has become widely used as a simple clinical index of obesity [59,229]. The distribution volume of ethanol is expected to be less in those who are obese compared with lean individuals, because ethanol is virtually insoluble in lipids and completely miscible in water. **Table 8** attempts to relate a person's degree of obesity as reflected in BMI with the expected distribution volume (V_d) of ethanol for that individual. However, few if any drinking studies in obese individuals have been done to verify these estimates of V_d reported in Table 8 [96]. With the worldwide epidemic of obesity, the pharmacokinetics of drugs in obese individuals, including ethanol, deserves careful attention and more investigations [31]. Controlled drinking experiments in both obese and emaciated individuals are needed to determine the impact of extremes of body composition on pharmacokinetic parameters β and rho.

4. Age and Volume of Distribution

The influence of a man's age (20–60 y) on the distribution volume of ethanol is illustrated in **Figure 7**, which shows mean blood-alcohol curves for 48 healthy men [123]. The BAC curve in the oldest age group (50–60 y) ran above the level of the others, with a higher value of C_0 and therefore a lower V_d in the elderly (dose/ C_0). The insert graph indicates a statistically significant decrease in V_d during aging as verified by analysis of

Table 8. Suggested values for the distribution volume of ethanol (Widmark's rho factor) depending on degree of clinical obesity as reflected in the body mass index (BMI)

Classification of obesity	BMI (kg/m ²)	Distribution volume of ethanol (L/kg) ^a
Under weight	<18.5	0.7–0.8
Normal weight	18.5–24.9	0.6–0.7
Pre-obese	25.0–29.9	0.5–0.6
Obese class I	30.0–34.9	0.4–0.5
Obese class II	35.0–39.9	0.3–0.4
Obese class III	>40	0.3–0.4

^a Values that might be expected.

variance ($p < 0.001$). The mean \pm SD for the 48 healthy men was 0.69 ± 0.043 , giving a 95% range from 0.604–0.776 L/kg, which is expected to be considerably wider if obese or emaciated individuals were included (**Table 9**). In this same study, the elimination rate of ethanol from blood (β parameter) was not related to a man's age between 20 and 60 y ($p > 0.05$).

In summary, during the process of aging the proportion of water per kilogram of body weight decreases, which results in a smaller body water space to dilute water-soluble drugs such as ethanol [32]. Since blood-water content remains more or less unchanged during ageing (80% w/w) this leads to a smaller volume of distribution in the elderly owing to a higher concentration of ethanol in blood for the same dose administered [83,123].

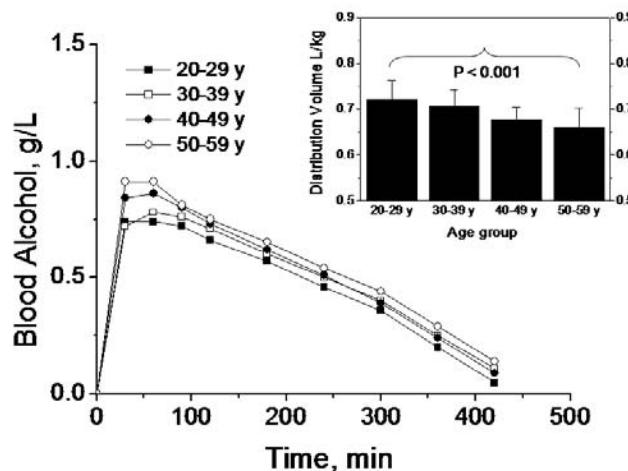


Figure 7. Mean blood-alcohol curves for four age groups of healthy men (20–59 y) after they drank a bolus dose of ethanol (0.68 g/kg) as neat whisky on an empty stomach. The insert graph shows that the rho factor or apparent distribution volume (mean \pm SD) decreases with advancing age. (Revised version of a figure appearing in the author's earlier publication [123].)

Table 9. Influence of age on the distribution volume of ethanol and the rate of elimination from blood in four age groups of healthy men after they drank neat whisky (ethanol 0.68 g/kg) after an overnight fast [109]

Age group	n	Distribution volume (L/kg) ^a	Elimination rate from blood (g/L/h) ^b
20–29 y	12	0.720 ± 0.042	0.126 ± 0.008
30–39 y	12	0.707 ± 0.036	0.122 ± 0.009
40–49 y	12	0.678 ± 0.026	0.130 ± 0.015
50–59 y	12	0.690 ± 0.043 ^c	0.126 ± 0.014 ^d

^a Widmark's rho factor, values shown are "mean ± SD".

^a Widmark's β factor, values shown are "mean ± SD".

^c Volume of distribution of ethanol decreases with age ($p < 0.001$).

^d No significant change in elimination rate from blood with age ($p > 0.05$).

C. Metabolism

Most of the ingested ethanol (90–98%) is removed from the body by oxidative metabolism, primarily in the liver, and a very small fraction (<1%) is conjugated via the -OH group to produce the nonoxidative metabolites ethyl glucuronide and ethyl sulfate [94]. The remainder of the dose administered (2–8%) is eliminated unchanged by filtration in the kidney and excretion in the urine [107]. Small amounts (1–2%) of ingested ethanol also undergo pulmonary excretion via the lungs and through the skin in the perspiration [26].

1. Hepatic Enzymes ADH and ALDH

The two main enzymes involved in the metabolism of ethanol are Class I alcohol dehydrogenase (ADH), located in the cytosol fraction, and Class II aldehyde dehydrogenase (ALDH) within the mitochondria [37,56]. A microsomal enzyme denoted CYP2E1 within the smooth endoplasmic reticulum is also involved in oxidative metabolism of ethanol [161]. Both ADH and CYP2E1 convert ethanol to acetaldehyde and this toxic metabolite is quickly oxidized to acetic acid by the action of low k_m ALDH [2,194]. The acetate produced during the catabolism of ethanol is transported away from the liver and is converted into the end products CO_2 and H_2O in the Krebs cycle [181,238]. The complete breakdown of ethanol liberates energy, actually 7.1 kcal/g (29.7 kJ) more than that obtained from ingestion of the same weight of protein and carbohydrate [160].

Figure 8 summarizes salient features of human metabolism of ethanol, including the oxidative and nonoxidative pathways and also the relative amounts excreted unchanged.

The hepatic metabolism of ethanol to acetaldehyde as well as subsequent conversion of the latter to acetic acid requires participation of the coenzyme nicotinamide adenine dinucleotide (NAD^+) [276]. During the oxidation of ethanol there is a shift in the redox state of the liver as NAD^+ is reduced to NADH , which has negative consequences for other NAD-dependent biochemical reactions. Among other things there is a well-documented risk for ethanol-induced hypoglycemia, hyperlactacidemia, and an accumulation of fat in the liver of heavy drinkers and alcoholics [163].

2. Polymorphism of ADH and ALDH

Both ADH and ALDH are polymorphic enzymes that exist in multiple molecular forms and the various isozymes differ in catalytic activity and specificity for substrates [56]. One of the most widely studied polymorphisms occurs with ALDH, which exhibits marked racial and ethnic difference in catalytic activity. In 40–50% of Asian populations the ALDH2 isoform has low or no enzymatic activity, and this genetic trait makes those inheriting the ALDH2*2 allele highly sensitive to drinking ethanol. These individuals flush in the face and neck, their blood pressure is lowered, and there is an increase in heart rate caused by an accumulation in the blood of acetaldehyde produced during oxidation of ethanol. However, this genetic polymorphism of ALDH2 does not influence the BAC reached after drinking or the rate of elimination of alcohol from the bloodstream [254]. After moderate drinking, the alcohol parameters β and rho in Asians were not much different from values observed in Caucasians and African Americans [1,241,246]. This means that the usual range of alcohol elimination rates (0.10–0.25 g/L/h) used for forensic purposes in Caucasians also applies to other racial groups.

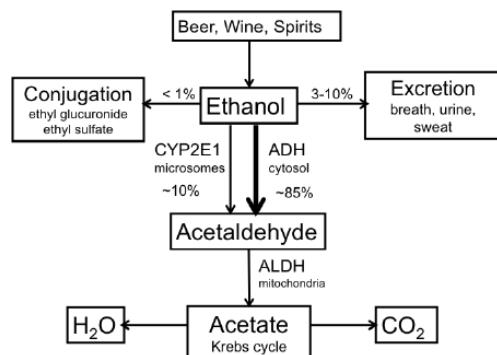


Figure 8. Schema of the fate of ethanol in the body illustrating both oxidative and nonoxidative metabolic pathways and the amounts of ethanol excreted unchanged. (Revised version of figures appearing in the author's earlier publications [94,99].)

3. Gastric ADH

The hepatic class I ADH has a low k_m (0.05–0.1 g/L) for ethanol as the substrate, which means that the enzyme is saturated after the first couple of drinks and ethanol is metabolized at a maximum velocity [131,132]. Another variant of the ADH enzyme (class IV) having a much higher k_m is located in the gastric mucosa. Some investigators consider that gastric-ADH plays a prominent role in presystemic or first-pass metabolism of ethanol [12,165]. The finding of a lower activity of gastric ADH in women and alcoholics was said to make these individuals more vulnerable to the negative effects of drinking alcohol [50,67]. Opinions differ about the quantitative significance of gastric ADH in first-pass metabolism of ethanol and experimentally this is difficult to distinguish from hepatic first-pass metabolism [154,155]. Much seems to depend on the experimental conditions, particularly the dose of ethanol, the fed/fasting state of the subjects, and use of certain prescription drugs, such as histamine H₂-antagonists or aspirin [68,155,247]. Very important in this connection is the speed of gastric emptying; the slower the absorption, the more potential for first-pass metabolism to occur in the stomach and liver [156,202]. From a large body of evidence, the present consensus is that if presystemic first-pass metabolism of ethanol occurs at all, then this is predominantly in the liver and not the gastric mucosa [5,27].

4. Microsomal Enzymes

The CYP2E1 enzyme mentioned above has a higher k_m for ethanol as substrate (0.6–0.8 g/L) and becomes more important in clearance of ethanol from the blood after moderate to heavy drinking [161,164,242]. Moreover, the CYP2E1 enzyme is inducible after periods of heavy drinking over weeks or months owing to a proliferation of the enzyme protein so that this pathway becomes more effective in the oxidation of ethanol and other drugs [216,240]. This explains the faster rates of ethanol metabolism observed in habituated individuals (alcoholics) during detoxification [76,137,204]. However, the daily intake of alcohol necessary to induce the CYP2E1 enzyme leading to a faster rate of metabolism has not been established in humans [201]. In alcoholics during detoxification, the average rate of elimination of ethanol from blood was 0.21 g/L/h, although in some individuals the elimination rate was no different from moderate drinkers [20,127].

The involvement of CYP2E1 in the metabolism of alcohol also accounts for a number of undesirable drug-alcohol interactions [161,242]. For example, the widely used over-the-counter analgesic and antipyretic drug acetaminophen (paracetamol) is converted into a poten-

tially toxic metabolite by CYP2E1 [140,148]. Accordingly, alcoholics with induced CYP2E1 activity should refrain from taking this medication because of the potential for hepatotoxicity [211]. The equation for CYP2E1-catalyzed oxidation of ethanol is shown below.



An enzyme located in the peroxisomes (catalase) can in theory accomplish the oxidation of ethanol, at least under *in vitro* conditions, whereas its role *in vivo* is questionable [38,276]. The oxidative reaction requires the presence of hydrogen peroxide and not enough of this substance is available *in vivo*. Therefore, for all practical purposes Class I ADH, Class II ALDH, and CYP2E1 are the enzyme systems mainly responsible for *in vivo* oxidative metabolism of ethanol in humans [39,40,159].

D. Excretion

A small fraction (2–10%) of the amount of ethanol absorbed into the blood is excreted unchanged with the breath, the sweat, and the urine [107,208]. Excretion is a first-order process, so proportionally more of the drug is eliminated when larger doses or higher concentrations are reached in the blood [136].

1. Urinary Excretion

The amounts of ethanol excreted in urine were studied after volunteers drank three doses of ethanol (0.51, 0.68, and 0.85 g/kg) on an empty stomach [100]. The volumes of urine voided at 60-min intervals were measured, and from the concentration of ethanol the amount of drug excreted by the kidney was calculated. The results are shown in **Table 10** and verify that only a small fraction of the dose of ethanol is cleared by glomerular filtration. For the highest dose of 0.85 g/kg, the urinary excretion of ethanol represented only 2% of the total amount ingested.

2. Pulmonary Excretion

The amount of ethanol excreted via the breath depends on lung ventilation rate and the underlying blood-ethanol concentration as the following hypothetical calculation shows. If the concentration of ethanol in pulmonary blood is 1.0 g/L and the blood/air ratio of ethanol is 2,000:1, then the alveolar air contains a concentration of 0.5 mg/L. In healthy individuals the respiratory minute volume at rest is about 6 L/min for a tidal volume of 500 mL and 12 breaths per min. Because ~30% of this breath is dead-space air and does not participate in gas exchange, the effective minute volume is 4.2 L/min or 252 L/h. Accordingly, at a BAC of 1.0 g/L (alveolar BrAC 0.5 mg/

Table 10. The amounts of ethanol excreted in urine (values shown are “mean \pm SD”) after increasing doses of ethanol taken in the form of neat whisky after an overnight (10 h) fast [100]

Ethanol ^a (g/kg)	Whisky dose ^{a,b} (g)	Amount excreted Gram	% of dose	Peak diuresis (mL/min)
0.51	1.5	0.29 \pm 0.119	0.70 \pm 0.290	2.56 \pm 1.45
0.68	2.0	0.44 \pm 0.246	0.80 \pm 0.399	3.41 \pm 2.26
0.85	2.5	1.00 \pm 0.427	1.55 \pm 0.501	6.12 \pm 2.08

^a n = 16 subjects per dose.

^b Dose unit: mL whisky/kg; whisky 40% v/v ethanol.

L) about 126 mg (0.5 mg/L \times 252 L) of ethanol is lost from the body per hour by exhalation. For a man with a body weight of 60–80 kg, this person eliminates about 6–8 g of 100% ethanol from the entire body per hour. So the 126 mg of ethanol lost in the breath represents only 1.5–2.0% of this total amount eliminated.

3. Sweat

A number of studies verify that trace amounts of alcohol are emitted from the body via the skin in perspiration, although the total quantity is trivial compared with the amount metabolized and excreted in urine and breath [25,26]. However, the analysis of ethanol in sweat has found practical applications as a way to monitor abstinence in patients who must refrain from drinking as part of a rehabilitation program or as a condition of their employment [176,239]. Subjects are fitted with a tamperproof skin patch, which collects perspiration emitted over various periods of time before the patch is removed and any alcohol it contains is analyzed as a way to monitor abstinence from drinking [209].

II. BLOOD-ALCOHOL PROFILES

Blood-alcohol curves in different individuals share certain common features (Figure 2). The BAC increases immediately after the start of drinking until a peak or maximum concentration is reached, usually within 60 min of finishing the last drink. After the highest point on the BAC curve (C_{max}), a rectilinear declining phase starts, during which time the BAC decreases at a more or less constant rate until alcohol is no longer measurable in the blood. The final shape of the BAC curve depends on the relative rates of absorption, distribution, and metabolism; Figure 2 gives examples of these intersubject variations. The peak BAC occurs earlier if the absorption is fast, often within 15 min after the end of drinking, although with a slow absorption the C_{max} might occur up to 120 min postdrinking.

A. Interindividual Variations

Blood-alcohol curves show large interindividual variations in C_{max} and t_{max} because these parameters are strongly dependent on the speed of gastric emptying, which differs widely between individuals depending on many factors. The magnitude of interindividual variation in shapes of BAC profiles from two experimental protocols with different doses of alcohol is illustrated in Figure 9. In these two experiments, alcohol was administered according to the individual’s body weight: 0.68 g/kg in 48 subjects (upper plot) or 0.40 g/kg in 22 subjects (lower plot).

Curve A on the upper plot shows an unusually rapid absorption of ethanol from the gut with a clear-cut overshoot peak resembling BAC curves obtained when ethanol is given by intravenous infusion [99]. The C_{max} of the curve is higher than expected for the dose of ethanol administered and body weight of the individual. Such curves are not unusual when neat spirits are consumed on

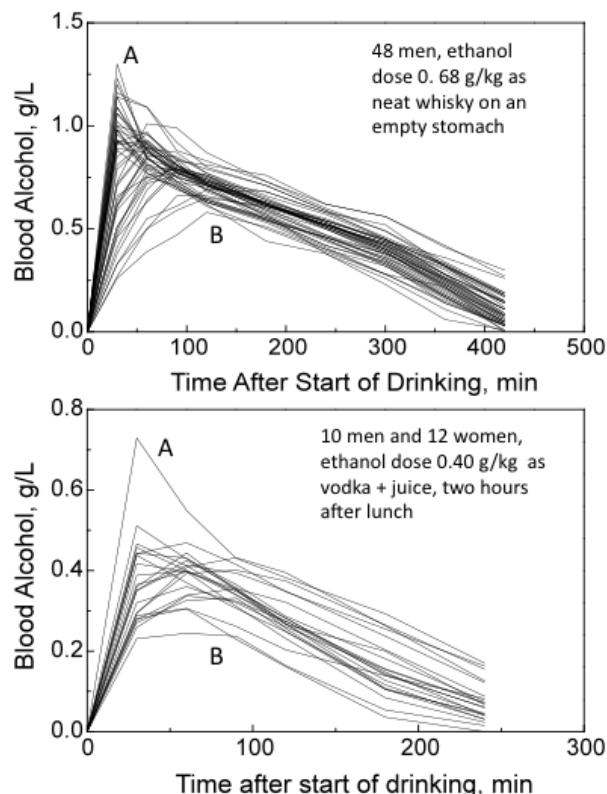


Figure 9. Intersubject variation in blood-ethanol profiles for two drinking scenarios. The upper plot represents BAC curves after healthy men (n = 48) drank neat whisky on an empty stomach; the lower plot shows BAC curves after (n = 22 subjects, 10 men and 12 women) drank a dose of 0.4 g/kg as 95 v/v ethanol diluted with orange juice (~10% v/v) ~2 h after eating a meal. (Revised version of a figure appearing in the author’s earlier publication [99].)

an empty stomach (overnight fast) as the pyloric sphincter opens to release alcohol into the duodenum and jejunum. The speed of absorption also determines the intensity of effects of alcohol on the brain, as reflected in subjective and objective signs and symptoms of intoxication [124,178,192].

Although alcohol was taken on an empty stomach, curve B in Figure 9 exhibits a much slower absorption phase with a lower C_{max} and a t_{max} occurring 100 min after end of drinking. Presumably in this case, drinking neat whisky irritated the gastric mucosa and triggered a pyloric spasm so that ethanol was absorbed into the bloodstream through the stomach wall and not the proximal gut, where the absorption surface area is larger. Long experience with evaluating hundreds of controlled drinking experiments speaks against making a definitive statement about the time to reach C_{max} in any individual case.

Figure 9 (lower part) is another example of large interindividual variation in BAC profiles in experiments with 10 men and 12 women who drank a smaller dose of ethanol (0.4 g/kg) 2 h after their last meal. Curve A and curve B on this plot also illustrates the large intersubject differences in C_{max} and t_{max} reflecting highly variable rates of absorption despite the use of standardized drinking conditions.

Blood-alcohol curves also show intraindividual variations varying from drinking occasion to drinking occasion [66,205,275]. In a four-part cross-over study the rate of elimination of ethanol from blood varied as much between as within individuals as shown by analysis of variance [116]. This confirmed the results from an older drinking experiment when three volunteers drank the same dose of ethanol (0.50 g/kg) on 10 occasions [224]. These observations speak against conducting drinking experiments in an attempt to reproduce blood-alcohol curves that might have existed in a drinking driver after the event. It is more prudent to work with a population average value of 0.15 g/L/h and a range from 0.10 g/L/h to 0.25 g/L/h, which should be appropriate for most individuals [99].

B. Dose-Response Relationships

The relationship between dose of a drug and the pharmacokinetic or pharmacodynamic response is a cornerstone in pharmacology and therapeutics. In practice such studies are restricted in terms of the quantities (doses) that can safely and ethically be administered to human volunteers. Accordingly, in the many controlled drinking experiments the peak BAC is appreciably lower than the BAC observed in cases of acute alcohol poisonings and alcohol impaired drivers [114].

Figure 10 shows BAC curves in 16 male subjects after 0.51 g/kg, 0.68 g/kg, or 0.85 g/kg ethanol was consumed as neat whisky after an overnight fast. The intersubject variations in BAC profiles are seen at each dose from the left part of the graph. An obvious increase in C_{max} , C_0 , and AUC occurs with higher doses of ethanol as shown by the right part of the graph. When even higher doses of ethanol were administered (1.05 g/kg) as neat spirits in a drinking time of 30 min, some of the subjects experienced nausea and vomited and the experiment was stopped.

The pharmacokinetic parameters of ethanol from this dose-response study are given in **Table 11**, which shows that both C_{max} and C_0 increase almost linearly with increasing dose, and AUCs were higher with higher doses (data not shown). The rate of elimination of ethanol from blood increased slightly with increasing ethanol dose from 0.11 to 0.15 g/L/h on average (**Figure 11**), but there was considerable overlap within each dose. The distribution volume of ethanol (V_d or rho), which depends on body composition, was not influenced by the dose of ethanol administered.

C. Intravenous Administration

In forensic science and toxicology, alcoholic beverages are taken by mouth (oral ingestion) and the ethanol these drinks contain reaches the systemic circulation after absorption from the gut. However, in some situations ethanol (8–10% v/v) might be administered by intravenous infusion, such as in emergency medicine when patients are treated with ethanol as an antidote to methanol or ethylene glycol poisoning [21]. After the intravenous route of administration the bioavailability of the dose is 100% because any first-pass metabolism that might occur in the liver or the stomach is avoided [5,35,171,232]. The AUC of the C-T profiles of drugs after oral and intravenous routes of administration provides basic information about the bioavailability of the active substance.

Figure 12 depicts a blood-alcohol curve in one subject after a small dose of ethanol (0.4 g/kg) was given by constant-rate intravenous infusion over 30 min. C_{max} occurred at the time the infusion pump was stopped and this was immediately followed by an abrupt decline in BAC, corresponding to a diffusion plunge as ethanol redistributed between the blood and other body tissues and fluids. This redistribution took about 30–60 min since the half-life of the diffusion plunge after a rapid intravenous infusion was estimated as 10 min [80].

Marked on the graph in Figure 12 is the start of the linear elimination phase as well as the hockey-stick portion of the BAC curve, which develops at low

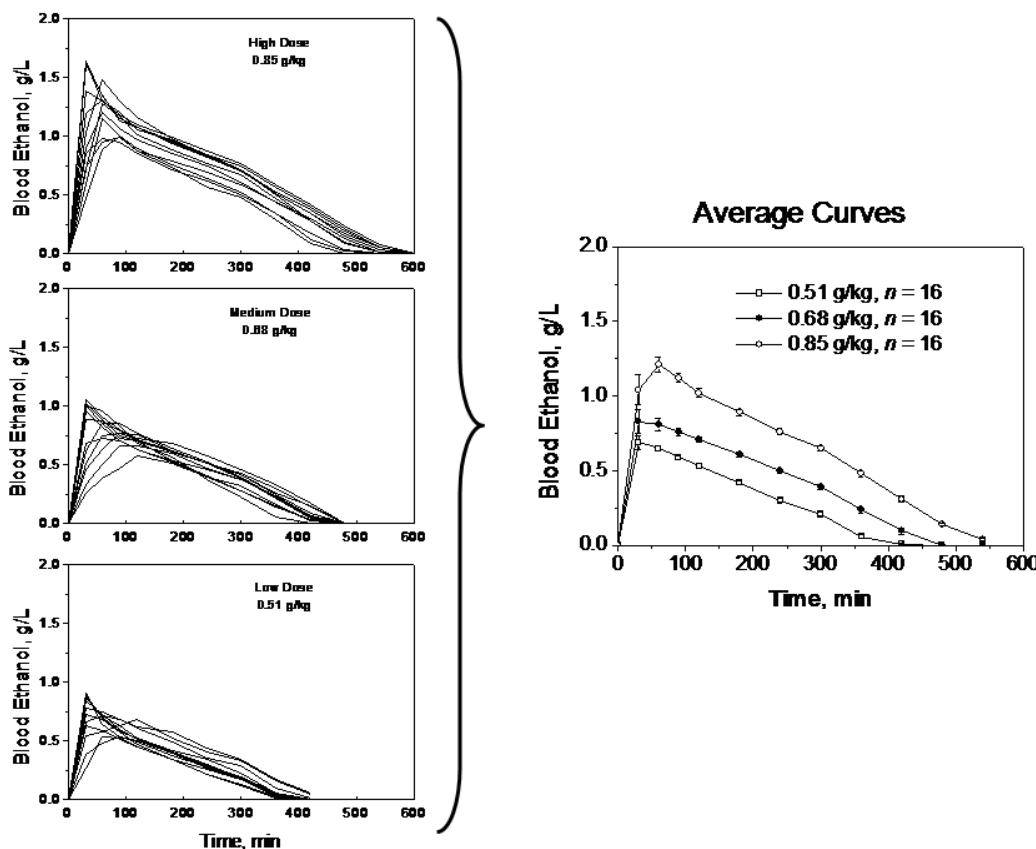


Figure 10. Comparison of blood-alcohol curves in healthy men who were given doses of ethanol to drink as neat whisky (0.51 g/kg, 0.68 g/kg, or 0.85 g/kg) on an empty stomach. The average BAC curves for these drinking conditions show an increase in C_{max} and area under the curves (AUC) with increasing dose. (Figures are constructed based on data collected in the author's laboratory).

Table 11. Dose-response study of ethanol pharmacokinetic parameters (values shown are “mean \pm SD”) in healthy men ($n = 16$ per dose) after they drank neat whisky on an empty stomach (10 h fast) in drinking times of 15 min (0.51 g/kg), 20 min (0.68 g/kg), or 25 min (0.85 g/kg)

Ethanol (g/kg)	Times (min)	C_{max} (g/L)	Mean t_{max} (min)	β -slope (g/L/h)	C_0 (g/L)	V_q or rho (L/kg)
0.51	15	0.75 ± 0.12	46	0.11 ± 0.01	0.75 ± 0.08	0.68 ± 0.06
0.68	20	0.91 ± 0.20	56	0.13 ± 0.02	0.98 ± 0.08	0.69 ± 0.05
0.85	25	1.31 ± 0.24^a	56	0.15 ± 0.01^a	1.34 ± 0.12^a	0.64 ± 0.06

^a Statistically significant differences by analysis of variance.

BAC (<0.2 g/L) as ADH enzyme is no longer saturated. Below this concentration, the C-T profile is curvilinear and ethanol is eliminated by first-order kinetics.

The intravenous route of administration avoids problems associated with variable gastric emptying but nevertheless, intersubject differences in BAC curves are still significant. **Figure 13** shows BAC curves after eight subjects received 0.3 g/kg ethanol by constant-rate intravenous infusion over 30 min.

The intersubject differences in intravenous BAC profiles, at least in part, stem from different proportion of fat to lean tissue and the fact that ethanol was administered per kilogram of body weight and not per kilogram of body water or lean body mass. After stopping the infusion of ethanol, variations in the BAC curves might also be attributed to different muscular activity on the part of subjects or variations in blood flow to tissue mass or inherent differences in hepatic enzyme activity.

D. Arterial-Venous Differences

Blood-ethanol concentration depends to some extent on where in the vascular system the sample is obtained from, whether an artery, a capillary, or a vein [228]. Studies have shown that arterial blood concentrations are higher during the absorption phase of the BAC curve and the venous blood concentrations are higher in the postabsorptive period [179,266]. Some of the ingested alcohol is taken up by tissue water, during each circulation of the blood, and initially muscle tissue is alcohol-free but holds a lot of water [152,184]. Accordingly, C-T profiles and some pharmacokinetic parameters will depend on whether arterial or venous blood was taken for analysis to plot C-T profiles for pharmacokinetic analysis.

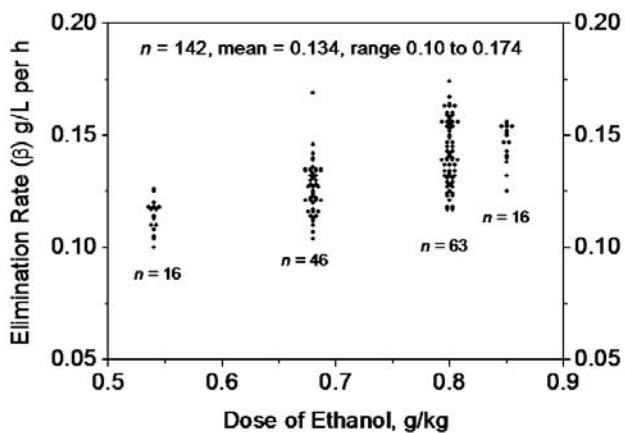


Figure 11. Relationship between dose of ethanol and the elimination rate from blood (β) showing considerable intersubject variation in this kinetic parameter and only minor effects of the dose of ethanol administered. (Figure is constructed based on data collected in the author's laboratory.)

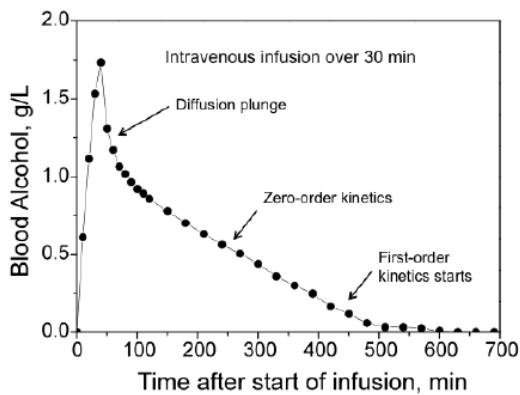


Figure 12. Typical blood-alcohol curve after the ethanol (0.3 g/kg, 10% v/v) was given as a constant rate intravenous administration lasting 30 min. Samples of venous blood were taken via an indwelling catheter at 5–10 min intervals after the infusion was started. The diffusion plunge, the phase of zero-order elimination and the start of first-order elimination kinetics when BAC is <0.2 g/L are marked on the plot. (Figure is constructed based on data collected in the author's laboratory).

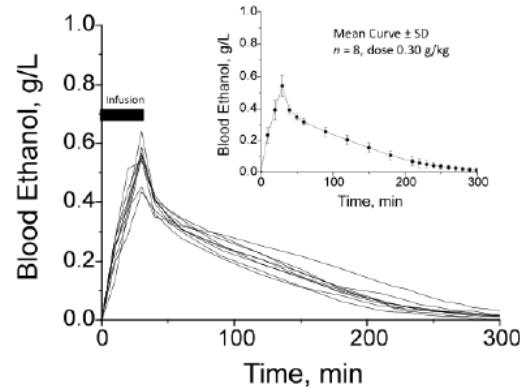


Figure 13. Concentration-time profiles of ethanol after constant rate intravenous infusions (0.30 g/kg, 10% v/v) demonstrating appreciable intersubject variation even when uncertainty of gastric emptying was eliminated by route of administration. The inset graph shows the mean BAC curve after this dose of ethanol. (Figure is constructed based on data collected in the author's laboratory.)

Figure 14 compares BAC profiles in arterial (radial artery) and venous (cubital vein) blood in two subjects when ethanol was given by oral or intravenous routes of administration [122,126]. Subjects either drank alcohol (0.8 g/kg) as a bolus dose or a smaller dose (0.4 g/kg) was given by constant-rate intravenous infusion over 30 min (lower part). The venous and arterial blood concentrations are clearly not identical in both plots, the A > V during absorption and V > A during the postabsorptive periods.

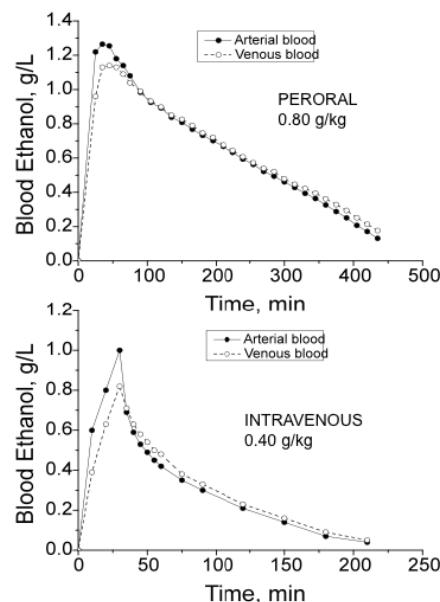


Figure 14. Concentration-time curves of alcohol in arterial (radial artery) and venous (cubital vein) blood after volunteers drank 0.8 g/kg ethanol (upper plot) or when ethanol (0.4 g/kg, 10% v/v) was given by intravenous infusion (lower plot) over 30 min. (Simplified versions of figures appearing in the author's earlier publications [122,126].)

After oral ingestion, A-V differences in alcohol concentration were maximum at the time the first blood sample was taken just 5 min postdosing [122]. Thereafter, A-V difference decreased gradually as the time after drinking increased so by about 90 min postdosing the A-V difference was zero. This marks the start of the postabsorptive phase of ethanol kinetics, and at all later blood sampling times the concentration of ethanol in venous blood was higher than in the arterial blood, owing to blood returning from peripheral tissues where metabolism takes place in the central compartment. The magnitude of A-V difference was more pronounced during the absorption phase compared with the postabsorptive period, as shown by the plots in **Figure 15**.

When ethanol was given as a constant rate intravenous infusion instead of by mouth, an A-V difference was established almost immediately and remained constant (~ 0.1 g/L) during the time alcohol was being infused [126]. Within 5 min of stopping the infusion pump, the A-V difference was abolished and at all later sampling times the concentration in venous blood exceeds that in the arterial blood (negative A-V difference). The pharmacokinetic parameters of ethanol C_{max} , t_{max} , etc., were slightly different when these were derived from analysis of venous or arterial blood as shown in **Table 12**.

The existence of an A-V difference deserves consideration when breath-alcohol test results are compared with venous BAC [169,179]. The time course of BrAC follows more closely the time course of arterial BAC than venous BAC, which means that the time course of A-V differences parallel venous BAC-BrAC differences. Temporal variations in venous BAC/BrAC ratios range from about 1,800:1 at 30 min after end of drinking to 2,100:1 by 60 min and are closer to 2,300:1 or 2,400:1 in the postabsorptive phase; these variations stem to a large extent from by A-V differences in concentration of ethanol. When very low BAC is reached (<0.2 g/L), the venous BAC/BrAC ratio might exceed 3,000:1, because arterial BAC reaches zero before venous BAC. The arterial BAC/BrAC ratio was more or less constant during the absorption, distribution, and elimination phases of ethanol kinetics [169].

Table 12. Comparison of pharmacokinetic parameters (values shown are “mean \pm SD”) of ethanol in arterial and venous blood after healthy men ($n = 9$) drank 0.6 g ethanol per kg body weight in 15 min [122]

Blood source	C_{max} (g/L)	t_{max} (min)	β -slope (g/L/h)	C_0 (g/L)	V_d or rho (L/kg)
Radial artery	0.98 ± 0.21	38 (35) ^a	0.12 ± 0.017	0.75 ± 0.007	0.80 ± 0.084
Cubital vein	0.84 ± 0.18^b	42 (35) ^a	0.11 ± 0.019	0.75 ± 0.008	0.81 ± 0.099

^a Values shown are “mean; medium”.

^b Statistically significant difference.

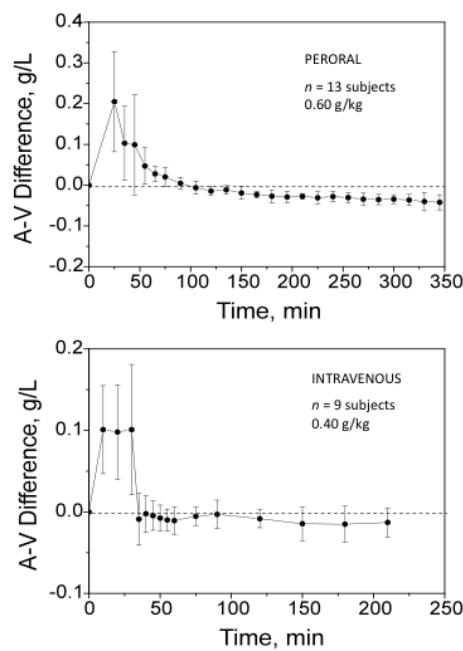


Figure 15. Time course of the mean differences in ethanol concentration (\pm SD) between arterial (A) and venous (V) blood samples after subjects drank 0.6 g/kg (upper part) or when 0.4 g/kg was given as an intravenous administration (lower plot) over 30 min. (Combined versions of figures appearing in the author’s earlier publications [122,126].)

E. Real-World Drinking Conditions

Most studies of the ADME of ethanol have involved the administration of moderate amounts of the drug as a bolus dose on an empty stomach, which is far removed from the real world, when people drink repetitively over several hours. In social situations, people drink alcohol in the form of beer, wine, or spirits, often together with food or snacks during social intercourse in pleasant surroundings. Limited information exists in the literature about shapes of BAC curves and the pharmacokinetics of ethanol under realistic social drinking conditions.

One notable exception was a paper by Zink and Reinhardt [277] in which the volunteers were allowed to drink massive amounts of alcohol more or less continuously

for up to 10 h. The BAC profiles were established unequivocally by frequent sampling and analysis of venous blood taken from an indwelling catheter at 15-min intervals during and after drinking ended. The original paper, which was in German, deserves close attention because of the pattern of drinking and the high BAC reached in a controlled study, which resembles forensic casework, such as alcohol-impaired drivers. The importance of the Zink and Reinhardt study prompted a reevaluation including replotting of all the BAC profiles and fresh pharmacokinetic analysis, and publication in an English language forensic journal [128]. Examples of such BAC plots for four volunteers from this unique study are shown in **Figure 16**.

Healthy male volunteers accustomed to heavy drinking drank the alcoholic beverage of their choice, in the company of a girlfriend or spouse, in a continuous drinking spree lasting 5–10 h. The BAC curves rose continuously during the drinking to reach very high peak values, similar to those observed in criminal casework. In some subjects the peak BAC occurred even before the last drink was finished. It seems likely that so much alcohol was already absorbed and distributed in body fluids and tissues, that the amount contained in the last drink was not sufficient to increase the BAC any further.

Large discrepancies were found between the observed peak BAC and the expected BAC based on the Widmark equation and the total amount of alcohol consumed, the drinker's body weight, and volume of distribution. The actual BAC was appreciably lower than the calculated BAC, assuming complete absorption and distribution of

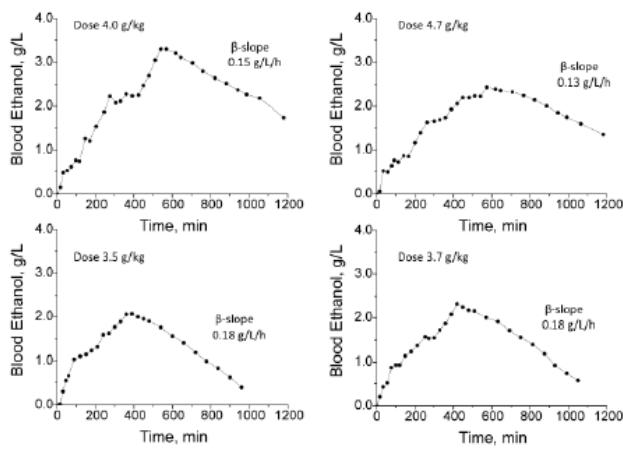


Figure 16. Blood-alcohol curves in four subjects after they drank massive amounts of ethanol under real-world conditions. The start of the postabsorptive phase is identified on the plots and zero-order elimination rates (β) were calculated as shown. (Revised version of a figure appearing in the author's earlier publication [128] and was constructed based on data appearing in Ref. [277].)

the entire dose. It is an open question what actually happened to the "missing alcohol" but most likely there was an appreciable first-pass metabolism or a more rapid metabolism taking place during the drinking period.

The rate of elimination of alcohol from blood when derived from C-T points on the postpeak parts of the curves were in the range expected for moderate drinking, namely from 0.15 to 0.25 g/L/h (Figure 16). The study by Zink and Reinhardt is unique to the forensic blood-alcohol literature and will probably never be duplicated considering the massive quantities of alcohol consumed by the volunteers.

F. Alcohol-Clamp Experiments

Another approach to pharmacokinetic studies of ethanol involves a so-called alcohol-clamp experiment [213,214]. This entails administering a priming dose of ethanol by intravenous infusion to reach a predetermined concentration in blood and then maintaining this concentration for several hours by continuous infusion of ethanol to balance the amount lost by metabolism. In this type of experiment, the steady-state concentration in blood is monitored by repetitive analysis of ethanol in the exhaled air [278]. Such an experimental design is depicted in **Figure 17**.

A good rule of thumb for the rate of infusion of ethanol to maintain a steady-state concentration in blood for a moderate drinker is 0.1 g/kg/h or 7 g/h for a person with a body weight of 70 kg. Quantitative breath-alcohol instruments are ideal for use in alcohol-clamp experiments because they are noninvasive and give immediate feedback about the arterial BAC, allowing adjustments to the infusion. Using the alcohol-clamp method, various factors that influence metabolism of ethanol, such as eating a meal, can be investigated without the confound-

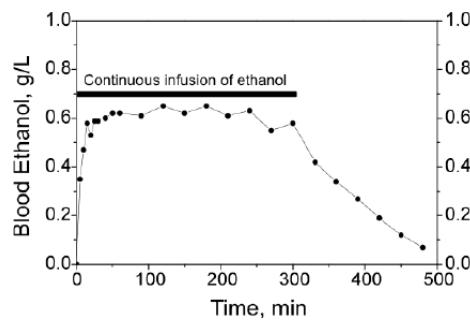


Figure 17. Example of a blood-alcohol curve obtained in an alcohol-clamp experiment whereby a priming dose of ethanol was given first followed by a constant rate infusion (~0.1 g/kg/h) to balance the amounts of ethanol lost by metabolism and excretion. (Figure is constructed based on data appearing in Ref. [278].)

ing influence of unpredictable rates of absorption from the gut and first-pass metabolism in the gastric mucosa or the liver [212].

An alcohol-clamp experiment was used to study the effect of nutrients on the rate of ethanol metabolism. After reaching a steady-state concentration in breath, the subjects ate a meal of known composition with differing proportions of fats, proteins, or carbohydrates [219]. During and after eating the meal, the infusion rate of ethanol had to be increased to maintain the same steady-state BAC, which suggests a food-induced acceleration in metabolism of ethanol. On stopping the infusion pump, the rate of elimination of ethanol from blood can be determined in the usual way from C-T data points and linear regression analysis.

III. THE WIDMARK EQUATION

The various types of blood-alcohol calculations often required in forensic science and legal medicine are dominated by the Widmark equation or some modification thereof. This assumes a one-compartment pharmacokinetic model with zero-order elimination from blood until BAC drops to reach a concentration of 0.2 g/L or less.

A. Basic Principles

From knowledge of chemical kinetics and reaction order, the rate equation for a zero-order process is given by the following differential equation:

$$-\frac{dC}{dT} = kC^0; \text{ simplifies to } -\frac{dC}{dT} = k (C^0 = 1)$$

Integration of the above between the limits of C_0 and C_t and rearranging gives:

$$C_t = C_0 - \beta t$$

The coefficient β in this equation is the zero-order elimination rate constant that defines the linear decrease in concentration of ethanol in blood per unit time, such as g/L/h. With drugs eliminated by zero-order kinetics, the concept of elimination half-life ($t_{1/2}$) is not a very useful parameter because it changes with the starting concentration. Replacing C_t in the above equation with $C_0/2$ and rearranging gives $t_{1/2} = C_0/2\beta$, which shows that $t_{1/2}$ is inversely proportional to the zero-order slope and directly proportional to the starting BAC or C_0 .

For drugs metabolized by first-order kinetics, $t_{1/2}$ is independent of dose and represents the time necessary for the concentration in blood or plasma, as well as the amount of drug in the body, to decrease by 50%. In practice ~97% of

a drug is eliminated from the body during a time corresponding to five half-lives.

The C_0 parameter in Figure 1 (y-intercept) represents the BAC obtained if the entire dose of ethanol was absorbed and distributed instantaneously into all body fluids and tissues without any metabolism or excretion occurring. Accordingly, the value of C_0 is higher than expected from dividing the amount ingested (A) by the person's body weight in kilograms (A/kg). Ethanol distributes into all body fluids and tissues according to their relative water contents and the blood, which is 78–82% w/w water, has a higher concentration of ethanol than the body, which is 50–60% w/w water.

The amount of alcohol absorbed and distributed in the body is easy to calculate from the concentration determined in blood by use of the Widmark equation and the important rho factor. This factor is multiplied by the person's body weight (kg) to give the reduced body mass (*die reduzierte Körpermasse*) as defined by Widmark, which represents the fraction of the body in which the drug is dissolved to give the same concentration as in the blood.

$$\begin{aligned} \text{BAC } (C_0) &= A / (\text{kg} \times \text{rho}) \\ A &= C_0 \times \text{kg} \times \text{rho} \end{aligned}$$

Because alcohol mixes with total body water without binding to plasma protein, the rho factor is related to the distribution of water between the blood and the rest of the body water.

$$\begin{aligned} \text{Rho} &= (\text{alcohol in body}) / (\text{alcohol in blood}) \\ \text{Rho} &= (\text{water in body}) / (\text{water in blood}). \end{aligned}$$

The elimination rate of alcohol from the entire body, sometimes denoted B_{60} , is obtained by dividing the dose (g/kg) by the extrapolated time to reach zero BAC (min₀) as shown in Figure 1. The resulting value is usually reported as g/h or g/kg/h and the same result is obtained as the product of $\beta \times \text{rho} \times \text{body weight}$.

The main source of uncertainty in the Widmark equation is the β and rho factors for the individual compared with reference values, usually taken as 0.7 for non-obese men and 0.6 for women. Moreover, spurious results of the calculations are obtained if blood samples are taken before absorption and distribution of the ethanol dose is complete. Any alcohol remaining unabsorbed in the stomach is not contributing to the BAC, so a Widmark calculation tends to overestimate the actual BAC. Moreover, if some of the alcohol undergoes first-pass metabolism in the gastric mucosa or the liver, this alcohol does not contribute to the measured BAC.

B. Forensic Pharmacokinetics

The Widmark formula has found four principal applications in forensic science and legal medicine:

- To estimate the amount of alcohol absorbed and distributed in all body fluids and tissues from the concentration determined in a blood sample;
- To make a back-extrapolation of a person's BAC from time of sampling blood to some earlier time, such as the time of driving;
- To estimate the total amount of alcohol a person has consumed after starting to drink until the time a blood sample was taken; and
- To estimate the BAC expected after drinking a known quantity of alcohol, thus making a forward prediction of the BAC based on a given drinking scenario.

C. Amount of Alcohol in the Body

The Widmark equation is widely used to calculate the amount of alcohol absorbed and distributed in all body fluids and tissues from the concentration determined in a sample of blood using the following equation.

$$A = C_t \times \text{weight (kg)} \times \rho$$

Where A is the amount of ethanol in grams absorbed and distributed in the blood and all body fluids, C_t is the concentration of ethanol determined in a blood sample (mg/g or g/kg), weight (kg) is the body weight of the individual, and ρ is the distribution factor for ethanol between the entire body and the blood. As discussed earlier, the value of the ρ factor depends on age, gender, and the individual's body composition, especially degree of fat to lean body mass.

It should also be noted that any alcohol remaining unabsorbed in the stomach when the blood sample was taken cannot contribute to the BAC. In principle, this BAC calculation should not be performed until at least 90 min has elapsed after the last drink. Neither does the Widmark equation consider any presystemic metabolism that might occur in the stomach or the liver or both locations.

D. Amount of Alcohol Consumed

The Widmark equation ($C_t = C_0 - \beta t$) represents the elimination of alcohol from blood during the postabsorptive phase and this is easily combined with the formula for the amount of alcohol in the body ($A = C_0 \times \text{kg} \times \rho$) by eliminating C_0 . This gives a useful formula that allows the total amount of alcohol consumed (A) to be calculated from time of starting to drink until the time of sampling blood.

$$A = \text{kg} \times \rho \times (C_t + \beta t)$$

The above equation gives reliable estimates provided that the alcohol is ingested as a bolus dose on an empty stomach and the blood sample is taken at least 90 min after end of drinking, so that alcohol is fully absorbed in all body fluids and tissues [74,252].

Similarly, an equation can be derived to allow calculating the BAC (C_t) expected after drinking a known quantity of alcohol (A):

$$C_t = A / (\text{kg} \times \rho) - (\beta t)$$

The major source of uncertainty in both these equations comes from the parameters β and ρ in relation to the values for a specific individual, which in practice is not known. A total uncertainty budget for use of the Widmark equation was published by Gullberg and this varied from 25–42% (2 \times CV) depending on the question posed, whether used to estimate the number of drinks consumed or the amount of alcohol in the body [72].

The elimination rate of alcohol from the entire body averages about 0.1 g/kg body weight per hour, corresponding to 7 g/h for a person weighing 70 kg. This parameter seems to be independent of gender because a lower ρ factor in women is compensated by the slightly faster rate of elimination from blood (β), so turnover rate of alcohol (B_{60}) given by the product of β and ρ is about the same for both sexes.

The total amount of alcohol consumed is easily derived from the BAC by first calculating the amount of ethanol in the body at the time of sampling blood ($A = C_t \times \text{kg} \times \rho$) and then adding on the amount eliminated from the time of starting to drink (0.1 g/kg/h). This gives a result in grams of 100% ethanol, which if required can be converted into the number of drinks consumed, whether beer, wine, or spirits, depending on their alcohol content. Note that concentrations of alcohol in alcoholic beverages are expressed as % v/v, which needs to be converted to % w/v by multiplying by the density of ethanol, 0.79 g/mL. Accordingly whisky, 40% (v/v); wine, 12% (v/v); and beer, 5% (v/v) correspond to 31.6% (w/v), 9.5% (w/v), and 4.0% (w/v), respectively.

E. Updating the Widmark Equation

The ρ factor depends on a person's age, gender, and body composition, and was first determined in the 1930s in healthy volunteers, aged 19–40 years, as the drinking subjects (20 men and 10 women). Body composition has changed and in today's society there is a high prevalence of obesity. This warrants reconsideration of the most appropriate ρ factor to use when blood-alcohol calculations are requested for forensic purposes.

The question of altered body composition prompted Watson, Watson, and Batt [258] to update the Widmark equation. They did this by establishing a multiple regression equation with TBW as outcome variable and a person's age, height, and weight as predictor variables. TBW was determined by isotope dilution and regressed on anthropometric measurements (age, height, and weight) for a large population of healthy subjects (458 men and 265 women). These equations and the associated residual standard deviations for men and women are given below:

For men: $TBW(L) = 2.447 - 0.09516 \text{ age(y)} + 0.1074 \text{ height(cm)} + 0.3362 \text{ weight(kg)}$; Residual standard deviation 3.78 L;

For women: $TBW(L) = -2.097 + 0.1069 \text{ height(cm)} + 0.2466 \text{ weight(kg)}$; Residual standard deviation 3.60 L

The TBW in liters derived from these equations was expressed as a percent of the person's body weight and related to the percent of water in whole blood to give a subject-specific rho factor. The percentage of water in blood varies little between individuals, although average values are slightly higher in women than in men because of gender differences in hematocrit.

Seidl et al. [230] determined water content of blood in 256 women and 273 men by heating a portion to dryness and reported mean \pm SD (range) of $79.5 \pm 0.97\%$ (77–82.8%) for women and $78.0 \pm 1.14\%$ (73.3–87.7%) for men. These percentages are in % w/w and should be multiplied by the density of blood (1.055 g/mL) to give the water content in units of mass/volume; 83.9% (w/v) for women and 82.3% (w/v) for men on average.

$$V_d = (\% \text{ water in body}) / (\% \text{ water in blood})$$

$$V_d = (TBW/\text{kg}) / 0.839 \text{ for women}$$

$$V_d = (TBW/\text{kg}) / 0.823 \text{ for men}$$

If an estimate of uncertainty in the calculation of TBW by the Watson, Watson, and Batt method is needed, this is given by $\pm (2 \times SD)$, which represents a 95% range of values.

F. Other Updates

A vast body of literature on forensic aspects of alcohol (alcohology) exists in German language journals, such as *Blutalkohol* and *Zeitschrift für Rechtsmedizin*. Use of the Widmark formula and the values of rho of 0.68 for men and 0.55 for women often resulted in higher BAC than those observed experimentally. This absorption deficit often amounted to 10–30% of the expected value.

The study by Seidl et al. [230] was an attempt to update the Widmark equation and they determined TBW by a noninvasive bioelectrical impedance method in 273 men and 256 women. The results provided modified values of the rho factor (V_d) tailored to the height and weight of the individual and values for men (r_m) and women (r_w) are given by the equations below:

$$r_m = 0.31608 - 0.004821 \text{ weight(kg)} + 0.004632 \text{ height(cm)}$$

$$r_w = 0.31223 - 0.006446 \text{ weight(kg)} + 0.004466 \text{ height(cm)}$$

Drinking experiments were performed in 30 women and 39 men to test the validity of the above rho values, and a much closer agreement was obtained compared with use of the Widmark rho values.

Another useful update of the Widmark rho factor involved a consideration of the person's BMI (kg/m^2) and percent fat content of the body. Information is usually available to calculate a person's BMI and percentage of body weight composed of fat-free mass and fat as a percentage of body weight are read from tables of body composition and various nomograms. This information can be used to calculate a subject-specific rho factor for use in blood-alcohol calculations [14,61].

G. Retrograde Extrapolation

The BAC used for prosecution in drunk-driving trials is not standardized and seems to depend on politics rather than traffic safety research. Sometimes the relevant BAC is that existing at the time of the offense (driving), whereas blood samples are obtained 1–2 h later. This raises the tricky question of back-calculating the person's BAC from the time of sampling blood to the time of driving, a process known as retrograde extrapolation or back-tracking [157,158,193].

Other jurisdictions enforce a so-called two-hour rule, which means that the measured BAC or BrAC can be used for prosecution if this is obtained within 2 h of the time of driving. If the blood sample for some reason is obtained later than 2 h, this requires that the prosecution calculate back to obtain the BAC at time of driving. Several important questions arise when back-extrapolations are performed in criminal trials.

1. First, if any alcohol was consumed after driving and before the blood or breath sample was taken, which would need to be considered before a back-calculation is done.
2. Second, the starting BAC should be the value after a deduction is made for uncertainty in the analytical method used (random and systematic errors).

3. Third, a range of elimination rates of alcohol from blood should be used, such as a mean of 0.15 g/L/h and a range from 0.10 to 0.25 g/L/h. In apprehended drivers, the mean elimination rate of alcohol was 0.19 g/L/h, although in criminal cases to give a suspect the benefit of any doubt, a low rate of elimination such as 0.1 g/L/h should be used.
4. Fourth, the BAC curve should be in the postabsorptive phase of metabolism at the time of driving and at the time that blood was sampled to motivate a back-calculation. This demands information about the drinking pattern, the time of last drink in relation to driving, and the amount of alcohol contained in the last drink. Depending on information provided about drinking, a correction might be needed for any ongoing absorption of alcohol.

The rate of absorption of alcohol from the gut is highly variable, making it uncertain whether a driver was in the postpeak phase of the BAC curve at the time of driving and at the time of blood sampling [91]. Experience has shown that the vast majority of people reach their peak BAC within 60 min after end of drinking a bolus dose. This time might be considerably shorter under real-world conditions with repetitive intake and when the last drink contained 12–14 g ethanol [53].

Assuming the person's BAC was in the postpeak phase at the time of driving and at the time of sampling blood, then a backward extrapolation is a simple mathematical exercise as shown below:

$$\begin{aligned} C_1 &= C_o - (\beta \times t_1) \\ C_2 &= C_o - (\beta \times t_2) \end{aligned}$$

In these equations, C_1 and C_2 are concentrations of alcohol in blood at sampling times of t_1 and t_2 on the declining phase of the BAC curve. Subtracting the two equations gives a general equation useful for retrograde extrapolation of BAC:

$$\begin{aligned} C_1 - C_2 &= \beta \times (t_2 - t_1); \text{ simplified to:} \\ C_1 &= C_2 + (\beta \times t_d) \end{aligned}$$

Where C_1 is BAC at time of offense, C_2 is BAC at time of sampling blood, and t_d is the differences in hours and β is the rate of elimination of alcohol from blood β in g/L/h.

If two or more hours have elapsed after the last drink when the blood was sampled, a back-extrapolation is a simple matter as shown by the following example.

A road-traffic crash occurred at 2:00 a.m. The driver of the car was injured and a passenger was killed. The driver was taken to hospital for treatment and a specimen of blood obtained at 5:00 a.m., which after analysis showed an ethanol concentration of 0.30 g/L after making a deduction for analytical error (uncertainty). The police wanted to know whether the driver was above the legal

limit for driving (0.50 g/L) at the time of the crash, which was 3 h before taking the blood sample. Investigations made by the police and statements from witnesses revealed that the driver had been drinking alcohol between 10:00 p.m. and 12:30 a.m. The last drink was finished at 12:30 a.m. before driving home at 1:00 a.m.

Social drinking over a time of 2.5 h makes it reasonable to assume that all the alcohol was absorbed and distributed in blood and other body fluids by the time of the crash 90 min after the last drink. This supports the assumption of a postabsorptive BAC at the time of crash (2:00 a.m.) as well as at the time of sampling blood (5:00 a.m.). Back calculation for 3 h at an elimination rate of 0.1 g/L/h shows that the driver's BAC at the time of the crash was at least 0.60 g/L (0.30 g/L + 0.10 g/L/h × 3), being over the legal limit.

The highest court in Germany ratified back-calculations of BAC in drunk-driving cases to within 2 h after the end of drinking if no information was available about the pattern of drinking and the amount of alcohol consumed in the last drink. Accordingly, if a blood sample was taken 4 h after the last drink, the measured BAC could be back-extrapolated over 2 h, which would increase the actual BAC by at least 0.2 g/L (elimination rate 0.1 g/L/h). If there was evidence indicating a normal social drinking pattern and standard drinks, the back-calculation is permissible in German courts up to 1 h after the end of drinking.

Drinking experiments were done to test the merits of back-calculation by taking blood samples at 1 h and 3.5 h after the last drink [237]. The BAC at 3.5 h was then used to estimate the BAC at 1 h assuming various rates of alcohol elimination from blood, such as 0.1 or 0.2 g/L/h. The BACs estimated 1 h postdrinking agreed well with measured values when an average elimination rate of 0.15 g/L/h was used and in no case was the BAC overestimated when a rate of 0.1 g/L/h was used.

The extent of the error in making a back-estimation of BAC was investigated in another study of 24 subjects, who consumed 0.71 g/kg ethanol as a bolus dose in 5 min [3]. The mean C_{max} for these drinking conditions was 1.16 g/L ($SD = 0.18$ g/L) and the mean elimination rate of ethanol from plasma was 0.186 ± 0.026 g/L/h ($\pm SD$). This suggests a 95% range of elimination rates from plasma of 0.134 to 0.238 g/L/h (mean $\pm 2 \times SD$). Note that these values should be lowered by about 15% to correspond to the elimination rates of ethanol from whole blood [93].

The actual plasma-alcohol concentrations at 4 h and 6 h postdosing were used to estimate values at 1 h postdosing. Calculations were made using the average plasma elimination rate of 0.186 g/L/h (experimental mean), 0.15 g/L/h, and 0.238 g/L/h. As expected, the most unbiased estimate was obtained using the average rate

(0.186 g/L/h) and the upper bound (0.238 g/L/h) gave the largest overestimate. The authors warn about using a single rate of elimination of alcohol from blood when back-calculations are done for legal purposes.

In a study designed to mimic a typical Swedish dinner party, the volunteers drank spirits, beer, and wine over 90 min at the same time they were served food; under these conditions BAC reached a plateau and remained unchanged for 1–2 h. An important finding from this study was that 15 min after the end of drinking, despite eating a meal, the measured BAC was 80% of the final peak BAC [125]. This verifies that alcohol is absorbed from the stomach even under conditions when drinking occurs along with a substantial meal.

The various problems overshadowing a back-extrapolation of BAC has prompted some jurisdiction to define the offense of drunk driving as the BAC or BrAC at the time of the test. What constitutes a reasonable time after driving is a matter for the courts. After involvement in a traffic crash, a driver might leave the crash scene or is transported to hospital for emergency treatment. Under these circumstances, a blood sample might not be obtained for several hours after the crash and at that time the BAC had dropped below the statutory limit. Obviously the police authorities want to know whether the person was over the statutory limit for driving at the time of the crash [95]. Back-extrapolation is often considered a dubious practice, because it requires certain assumptions about the ADME of alcohol and these assumptions need to be carefully explained to the court in each case.

H. Prospective Estimation

Forensic scientists are sometimes asked to calculate a person's BAC based on information provided about the number of drinks consumed and the age, gender, and body weight of the individual. The Widmark equation is commonly used in such calculations, but adjustments might be necessary to allow for less than 100% bioavailability of the dose of ethanol ingested.

Experiments have shown (Figure 3) that when alcohol is ingested together with or after a meal, the BAC curves run on a lower level and the apparent distribution volume (rho factor) calculated as dose (g/kg)/C₀ is abnormally high. If an expected BAC is calculated by use of the Widmark equation by plugging in a rho factor for the fasting state (0.68), the resulting BAC will be falsely high. Blood-alcohol parameters derived from BAC curves in the same individuals (cross-over design) after they drank ethanol (0.8 g/kg) in 30 min either on an empty stomach or after eating a standardized breakfast are shown in **Table 13**.

The food-induced lowering of C_{max} and C₀ as well as an increased t_{max} and abnormally high rho factor (dose/C₀) were statistically significant ($p < 0.001$). The rho factor (V_d) for ethanol is a physiological parameter that depends on an individual's age, gender, and body composition, such as degree of adiposity. The rho factor can only take certain values and will not change because alcohol was ingested with food compared with empty stomach drinking conditions. Instead, what happens is that part of the dose of alcohol fails to reach the systemic circulation in the fed state, probably because of first-pass metabolism by enzymes in the gastric mucosa or the liver. The clearance of ethanol from blood might also have been faster because of food-induced increase in liver blood flow [79,223]. Otherwise, some part of the dose of ethanol might be bound to constituents of the food, such as the amino acids, and released over several hours at a slower rate than the actual elimination rate of ethanol from blood (0.15 g/L/h). Accordingly, the BAC curve would show a declining phase even when alcohol was still being absorbed from the stomach at a rate less than 0.15 g/L/h.

If the rho factor for fasting conditions (e.g., 0.68 in men) is used to calculate C_t by means of the Widmark equation when alcohol was ingested with food, the C_t is overestimated.

$$A = C_t \times kg \times rho$$

$$C_t = A / (kg \times rho)$$

Table 13. Mean blood-alcohol parameters obtained in a cross-over design experiment with 12 healthy subjects and dose of ethanol of 0.80 g/kg body weight in 30 min either on an empty stomach (overnight fast) or immediately after eating a standardized breakfast [117]

Drinking condition	C _{max} (g/L)	t _{max} (min)	C ₀ (g/L)	V _d or rho (L/kg)	Min ₀ (min)	β-slope (g/L/h)	B ₆₀ (g/kg/h)
Fed	0.62	120	0.97	0.82	393	0.15	0.123
Fasting	0.96 ^a	45 ^a	1.16 ^a	0.69 ^a	495 ^a	0.14	0.097 ^a

^a Statistically significant difference between fed and fasting states.

The above equation can be modified by lowering the dose of alcohol by 10–20% to allow for presystemic metabolism if drinking had taken place together with or after a meal.

$$A \times f = C_1 \times \text{kg} \times \text{rho}$$

$$C_t = (A \times f) / (\text{kg} \times \text{rho}) - (\beta \times t)$$

The factor “f” is less than unity (1.0) and compensates for the lower bioavailability of the ethanol dose in the fed state. Values of 0.9 or 0.8 might be considered depending on size of the meal and other considerations, as shown in the following example.

Assume a young healthy male subject who drank ethanol (0.80 g/kg) immediately after eating breakfast. What BAC would be expected at 90 min postdosing? With a rho factor of 0.68 and an elimination rate of ethanol from blood of 0.15 g/L/h the estimated BAC (C_v) according to the Widmark equation is 0.95 g/L. Results from many drinking studies with food show a reduced bioavailability of the dose and requires some adjustment to the equation, such as, by use of the “f” factor assumed to be 0.80. The estimated BAC (C_v) at 90 min postdosing is now 0.72 g/L, which was in very good agreement with the value observed experimentally of 0.75 g/L.

The bioavailability of ethanol is 100% when the dose is given intravenously and close to 100% when given as a bolus dose as neat spirits on an empty stomach (overnight 10-h fast). Both C_{\max} and AUC are appreciably lower when ethanol is consumed together with or after a meal (Figure 3, Table 13). Furthermore, in forensic casework the reliability of blood-alcohol calculations is questionable when based on information provided by a person charged with a serious criminal offense, such as drunken driving. These individuals are rarely truthful about how much alcohol they had consumed and over what time period, although this is something for the courts to ponder over.

I. Hip-Flask and Laced Drinks

The hip-flask drink, also sometimes referred to as the glove-compartment drink, implies the consumption of alcohol after driving or after involvement in a traffic crash. This legal-defense argument has become increasingly common in some nations and has sometimes resulted in acquittals or a lesser charge being brought if graded penalties exist [89,234]. In the United Kingdom the onus of proof in hip-flask cases rests on the suspect and his or her lawyers, who have to demonstrate to the court that it was alcohol in the hip-flask drink that caused the person’s BAC to be over the legal limit for driving.

In other nations the onus of proof in after-drink cases rests on the prosecution, and unless the suspect is taken sitting behind the wheel there is a strong likelihood that he or she will claim consumption of alcohol after driving. Such claims complicate the prosecution of offenders, and expert witnesses are required to evaluate the truthfulness of statements about drinking after driving and what it means for the BAC at time of driving. The following example illustrates such an after-drink case.

After a minor road traffic crash, the driver of a car took two swigs of whisky from a bottle in the hip pocket of his jacket, allegedly to calm his nerves. A roadside breath alcohol test on the driver was positive (statutory limit 0.50 g/L in blood). A blood specimen taken 90 min later contained 1.0 g/L ethanol after a deduction was made for uncertainty. At trial the question about drinking after driving arose and the defense and prosecution attorney accepted that two swigs of whisky corresponded to 120 mL (40%, v/v; or 31.6%, w/w, or 38 g ethanol (100% v/v). The man’s body weight was 90 kg and because he was fairly obese (BMI = 30), instead of a distribution volume of 0.7 L/kg it was accepted that 0.6 L/kg was more appropriate. The Widmark equation shows that the highest BAC from the 38 g ethanol in the after drink is 0.70 g/L [38/(90 × 0.6)]. Over the 1.5 h elapsed after drinking two swigs of whisky some of this is eliminated by metabolism in the liver. At slow (0.10 g/L/h) or rapid (0.25 g/L/h) rates of elimination, the BAC decreases by between 0.15 g/L and 0.38 g/L. The after-drink therefore accounts for a BAC of 0.55 g/L (0.70 – 0.15) or 0.32 g/L (0.70 – 0.38), depending on the rate of alcohol elimination from blood. Before taking the two swigs of whisky after driving the BAC at time of driving was either 0.45 g/L (1.0 – 0.55) or 0.68 g/L (1.0 – 0.32). If none of the alcohol contained in the after-drink was metabolized, which would benefit the suspect, the BAC at time of the crash would have been 0.30 g/L (1.0 – 0.70).

In this example, complete absorption and distribution of the alcohol contained in the hip-flask drink is assumed, which is obviously to the person’s advantage [88]. If in reality some of the alcohol remained unabsorbed at the time, this cannot contribute to the BAC. If an adjustment is made to allow for metabolism of some of the alcohol contained in the after drink, then a low elimination rate of 0.1 g/L/h is recommended in criminal cases [99].

A closely related argument in DUI litigation is the “laced drink” defense, whereby the suspect alleges that his drink was spiked with vodka or some other strong alcoholic drink without altering the taste [147]. It was the extra alcohol from the vodka that caused the person’s BAC to be over the legal limit when driving. The BAC expected from the amount of vodka added to the beer is calculated by the Widmark equation and compared with the observed BAC. Also, in the laced-drink calculation

some allowance for metabolism of alcohol in the vodka seems justified, although this would not be beneficial to the defendant.

IV. OTHER PHARMACOKINETIC MODELS

A. First-Order Kinetics

Most recreational drugs as well as prescription medication are eliminated from the body according to first-order kinetics [221]. This implies, among other things, that the rate of change in drug concentration in blood or plasma is directly proportional to the concentration existing at that time. The general rate equation for a first-order reaction is given below:

$$\begin{aligned} dC/dt &= -kC \\ dC/C &= -kdt \end{aligned}$$

If this equation is integrated from $C = C_0$ at $t = 0$ and $C = C_t$ at time t , one obtains the exponential function $C_t = C_0 e^{-kt}$ corresponding to the C-T plot in **Figure 18** (left part). Taking logarithms of this equation gives:

$$\ln C_t = \ln C_0 - k_1 t$$

Plotting $\ln C$ against time t gives a linear function as shown in Figure 18 (right part). In this equation the coefficient, k_1 , is a first-order rate constant and $\ln C_0$ is the y-intercept.

The relationship between the half-life and the elimination-rate constant for a first-order reaction is obtained by substituting $C_t = C_0/2$ into the above equation and rearranging to give:

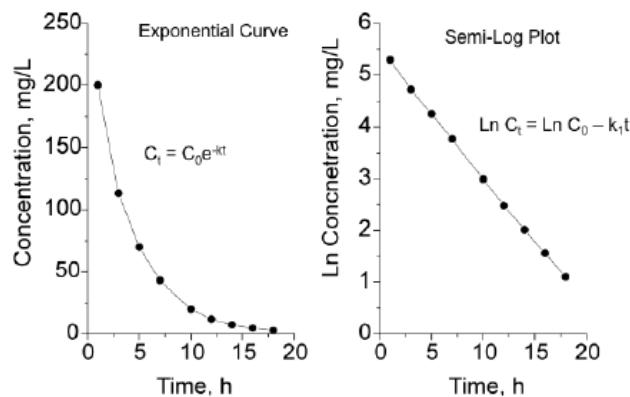


Figure 18. Example of the concentration-time profile of a drug when elimination follows first-order kinetics with an exponential decline (left part) and linear decline after concentrations of the drug were converted to natural logarithms (right plot). (Figure is constructed by the author based on theoretically calculated data.)

$$\ln C_0 / 2 = \ln C_0 - k_1 t_{1/2}$$

$$k_1 t_{1/2} = \ln C_0 - \ln C_0/2$$

$$k_1 t_{1/2} = \ln 2$$

$$t_{1/2} = \ln 2/k_1 \text{ and because } \ln 2 = 0.693$$

$$t_{1/2} = 0.693/k_1$$

There is some suggestion, although not very convincing and with scant scientific support, that at sublethal concentrations of ethanol in blood of 4–5 g/L (0.4–0.5 g/100 mL) the elimination kinetics might be first-order rather than zero-order [81,170]. This was first demonstrated in hospital emergency patients undergoing detoxification, but only a few blood samples were available for determination of ethanol, making a proper kinetic analysis very difficult [146]. Moreover, at such very high BAC proportionally more alcohol is eliminated via the breath and urine because these are first-order kinetic processes.

B. Michaelis-Menten Kinetics

Evidence that the elimination kinetics of ethanol from blood might depend on the concentration in blood began to emerge in the early 1950s, coinciding with the development of more sensitive enzymatic methods of analysis. With these so-called ADH methods, the concentrations in blood and the BAC curves could be followed to much lower levels. Other studies showed that the disappearance rate of ethanol from blood (β) was faster after subjects drank larger doses of ethanol and the zero-order slope tended to be steeper at higher starting BAC [265]. These observations did not fit with the postulate of zero-order elimination kinetics of ethanol [215]. For drugs metabolized by saturation kinetics, the area under the curve and the concentration of drug in blood changes more than proportionally with an increase in dose, which for some drugs has serious clinical implications [173,250,251].

Michaelis and Menten (M-M), a man and woman respectively, hypothesized the existence of an enzyme-substrate complex as a scientific basis to understand enzyme-catalyzed biochemical reactions in 1913 [190]. The M-M equation indicates that the velocity of the enzymatic reaction increases with substrate concentration, but only up to a certain limiting value. This rate is denoted V_{max} and at higher concentration the enzyme is saturated with substrate and the reaction (oxidation) proceeds at maximum velocity. The substrate concentration at half maximum velocity ($V_{max}/2$) is denoted k_m and is a measure of the affinity of the enzyme for the substrate, being referred to as the Michaelis constant [253].

$$-dC/dT = (V_{max} \times C) / (k_m + C)$$

For drugs eliminated by M-M kinetics the reaction rate ($-dC/dt$) is a function of both the substrate concentration (C) and the theoretical maximum reaction velocity V_{max} , and is inversely proportional to k_m , the Michaelis constant for the particular enzyme involved. As substrate concentrations increase, binding sites on the enzyme become saturated and the enzymatic reaction then occurs at maximum velocity (V_{max}). **Table 14** illustrates the relationship between substrate concentration (BAC) and the rate of elimination from blood with different affinity of the enzyme for substrate as reflected by k_m values of 0.025, 0.05, or 0.10 g/L and a maximum reaction velocity of 0.22 g/L/h.

The application of the M-M equation to experimental C-T data for ethanol was first demonstrated by two Danish scientists, Lundquist and Wolthers, in 1958 [175]. They obtained a good mathematical fit for ethanol concentrations-time profiles on the linear and the curvilinear portions of the curve. In their article, the Michaelis constant for ethanol (k_m) was reported to be 2.03 mmol/L (0.09 g/L) and the maximum reaction velocity V_{max} was 0.22 g/L/h; the latter corresponds to the zero-order slope of the elimination phase [175].

In the late 1970s, John G. Wagner and his collaborators applied the M-M equation to blood-alcohol profiles and found convincing evidence of dose-dependent saturation kinetics [251,253]. The C-T plot looked more like a hockey stick rather than a straight line when these were plotted from high to very low BAC (<0.1 g/L). The relevance of considering such low BAC (<0.2 g/L) in routine forensic investigations of drunken drivers or alcohol-related trauma is questionable.

Figure 12 gives an example of a BAC curve when ethanol as given by intravenous administration and when blood samples were taken at short intervals of time down to very low BAC. The hockey-stick shape of the C-T profile in the late postabsorptive phase of the curve is clearly evident.

Table 14. Relationship between substrate concentration (BAC) and elimination rate of ethanol from blood for a capacity-limited enzymatic reaction with a V_{max} of 0.22 g/L/h and three different Michaelis constants (k_m values) for the oxidizing enzyme (0.025 g/L, 0.05 g/L, and 0.10 g/L)

Substrate conc. BAC (g/L)	Elimination rate (g/L/h) at k_m value 0.025 g/L	0.05 g/L	0.10 g/L
0.10	0.18	0.15	0.11
0.20	0.20	0.18	0.16
0.25	0.21	0.20	0.20
1.00	0.21	0.21	0.20
1.50	0.21	0.21	0.21
2.00	0.21	0.21	0.21

Depending on the concentration of substrate (C), the M-M equation collapses into two limiting forms. When C is high compared with k_m , the M-M equation becomes:

$$-dC/dt = V_{max}$$

When the substrate concentration (C) is low compared with k_m as the BAC drops below 0.1 g/L, the M-M equation becomes:

$$-dC/dt = (V_{max} \times C)/k_m = k_1 C$$

In the above equation $k_1 = V_{max}/k_m$ and is a first-order elimination rate constant being directly proportional to the substrate concentration as shown in **Figure 19** (right part). The values of V_{max} and k_m can be determined graphically by using an integrated form of the M-M equation as described in detail elsewhere [251,265]. Strictly speaking, the M-M equation is designed to apply to a single enzyme system and assumes that substrate concentrations are determined at the site of the enzymatic reaction—that is, in the liver—but this is never the case in practice. A further complication is the existence of multiple forms of ADH with different k_m and catalytic activity as well as the contribution from other enzymes, such as CYP2E1 having a higher k_m (close to 0.6–0.8 g/L). This makes values of V_{max} and k_m hard to rationalize in relation to a single enzymatic reaction.

Nonlinear M-M kinetics can be considered as encompassing zero-order, which operates at moderate concentrations of substrate, and first-order kinetics that dominate at low substrate concentrations. Although the

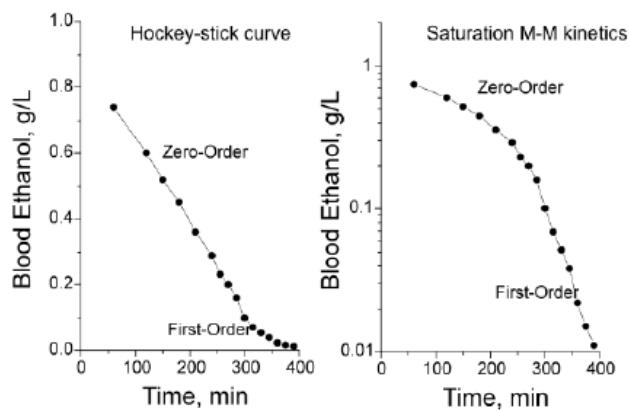


Figure 19. Example of the concentration-time profile of a drug eliminated by nonlinear saturation kinetics showing a pseudolinear elimination phase at high concentration and a nonlinear declining phase at low concentration (left plot). After logarithmic transformation of drug concentrations the zero-order and first-order elimination kinetics are indicated (right plot). (Figure is constructed by the author based on theoretically calculated data).

M-M kinetic model provides a good fit to the entire postabsorptive elimination phase, spanning from high to very low BAC (Figure 19, left part), in forensic casework there is not much practical benefit compared with a one-compartment model with zero-order elimination kinetics.

C. Pharmacokinetic Software

A number of different computer programs are intended to simplify making a pharmacokinetic analysis of concentration-time data and some of these programs are fairly sophisticated, e.g., WinNonLin, PharmaCalc, and Boomer [30,69]. Although this type of software is mainly intended for research and development in the pharmaceutical industry, there are obvious applications in clinical research and forensic science, including human pharmacokinetics of ethanol and other drugs [198]. These software packages contain curve-fitting algorithms and other procedures to evaluate concentration-time data for various input variables, such as dose, dosage interval, drug formulation, and route of administration. The reliability of results generated by pharmacokinetic software and the uncertainty inherent in the parameters β and rho depends very much on the reliability of the C-T data used as input variables. Accurate and precise analytical methods and careful consideration of preanalytical factors are prerequisites to avoid the problem commonly known as “garbage in, garbage out.”

The use of alcohol calculations in education and teaching of public health workers or the training of police officers and forensic scientists is increasingly common [43]. For this purpose, nomograms or so-called “know your limit” tables exist whereby the user gets an estimate of BAC from information about body weight, gender, and number of drinks consumed. Caution is necessary when results from these alcohol nomograms are used to decide whether a person is “safe to drive” or is below a statutory alcohol limit, and a confidence-limits approach is recommended [8].

More sophisticated software packages have become available especially designed for making blood-alcohol calculations based on a person’s age, body weight, and gender, the pattern and duration of drinking, the type of drinks consumed, and whether taken with or without food. Options exist for plotting the “expected” BAC curve based on certain assumptions about β and rho. Examples of such programs include Easy-Alc, AlcoTrace, and AlcoGraph, although the validity and usefulness of this type of computer software by comparing results with alcohol-drinking experiments is hard to find in the literature [210,218].

Some programs and BAC calculators are available gratis over the Internet and operate together with spreadsheet programs, such as Microsoft Excel. The advantage

and limitations of this computer software compared with a pen and paper and a hand-held calculator needs to be demonstrated. In most forensic situations, only a single measurement of the person’s BAC or BrAC is available, which precludes the use of curve-fitting algorithms to derive pharmacokinetic parameters. Furthermore, information provided by a defendant in a DUI trial about number of drinks consumed, etc., is not sufficiently reliable for making blood-alcohol calculations.

A computer program (PKQuest) was useful in pharmacokinetic modeling and was applied to intestinal absorption of ethanol and first-pass metabolism [152,153]. The same program was used to compare the clinical pharmacokinetics of ethanol in venous and arterial blood based on experimental data, and the results were very satisfactory [152].

D. Pharmacokinetics in Alternative Specimens

In the field of clinical pharmacology and TDM, drugs are mostly analyzed in plasma or serum, whereas in forensic science and toxicology drugs are determined in whole blood. Chemicals and other substances don’t necessarily distribute evenly between the plasma and the erythrocyte fractions of whole blood, owing to varying degrees of protein binding and the relative solubility in lipids compared to blood water [112,121].

Studies have shown that plasma and serum are composed of ~92% w/w water compared with whole blood, which is 80% w/w water, which suggests a plasma/blood distribution ratio of water and ethanol of 1.15 to 1 (92/80 = 1.15) [90]. The plasma/blood distribution ratio of ethanol varies between and within individuals depending on factors that influence the water content of the specimens, such as the degree of hydration, hematocrit, and lipid content of serum, such as hyperlipidemia [9,231].

The different amounts of water in different biofluids means that C-T profiles of ethanol and pharmacokinetic parameters differ depending on whether C-T profiles were constructed from plasma or whole blood [113]. The slope of the declining phase profile is expected to be steeper for plasma compared with whole blood, resulting in a higher C_0 and thus a lower V_d (dose/ C_0) for ethanol. In some published studies, BACs are mentioned but on closer inspection it becomes obvious that the investigators had determined ethanol in plasma, which obviously impacts on the pharmacokinetic parameters [149].

There is a lot of interest among forensic toxicologists for use of alternative and less invasive biological specimens, such as saliva, for analysis of drugs and toxins [70].

Figure 20 compares C-T profiles of ethanol in saliva, breath, urine, and whole blood after 21 men drank 0.68 g/kg ethanol as a bolus dose on an empty stomach [105,107].

The pharmacokinetic parameters derived from individual C-T profiles of ethanol determined in blood, saliva, urine, and breath are compared in **Table 15**.

The vast majority of pharmacokinetic studies of ethanol are based on sampling and analysis of blood, either capillary (fingertip), venous, or arterial samples. By contrast, most forensic alcohol testing today involves the use of evidential breath-alcohol instruments [73]. Translating the measured BrAC into the presumed BAC is not recommended because the BAC/BrAC ratio is not constant but varies depending on the stage of ethanol metabolism [108]. The concentration of alcohol in breath is more closely related to the arterial BAC rather than the venous BAC, as discussed earlier, even though statutory limits of blood alcohol for driving are based on analysis of venous blood [169].

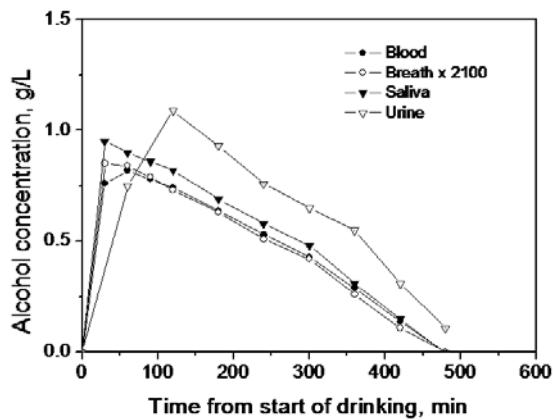


Figure 20. Mean concentration-time profiles of ethanol in blood, breath, urine, and saliva in experiments with 21 men after they drank a moderate dose of ethanol (0.68 g/kg body weight) as neat whisky on an empty stomach. The breath-alcohol concentrations are here multiplied by 2,100 to allow display on the same C-T plot and direct comparison with other body fluids. (Revised version of a figure appearing in the author's earlier publication [94].)

The increasing use of breath-alcohol instruments in law enforcement calls for studies of the ethanol elimination rates based on repetitive breath samples and pharmacokinetic parameters derived from breath-alcohol profiles. **Table 16** shows a good overall agreement between mean and range of elimination rates of ethanol from breath (mg/L/h) in three studies and two types of breath analyzer [48,109,206]. The slopes of the declining phase of the BrAC profiles were slightly steeper for females compared with males, in each study, which agrees with findings based on BAC curves [45]. The rate of elimination of ethanol from breath should not be converted into the elimination rate from blood using a constant BAC/BrAC ratio, because this ratio varies depending on time after drinking when the tests were made [77].

Breath-alcohol instruments are now used worldwide for legal purposes as an alternative to blood sampling as evidence for the prosecution of drunken drivers. For this purpose, statutory limits of BAC exist, such as 0.08 g/210 L in the United States or 35 µg/100 mL in the United Kingdom (Table 4). Use of breath-alcohol testing for evidential purposes has prompted studies of inter- and intraindividual differences in C-T profiles of ethanol derived from analysis of exhaled air [222]. In this connection, the effect of eating a meal before drinking resulted in a lower C_{max} and C_0 as well as a smaller AUC for breath-alcohol curves compared with the fasting state, being in good agreement with blood-alcohol curves [134].

Other body fluids used to construct C-T profiles of ethanol include lumbar cerebrospinal fluid and sweat, which show an appreciable time-lag compared with blood-alcohol profiles [25,26]. The CSF and sweat curves were found to have a higher C_{max} and later-occurring t_{max} compared with BAC [60,185]. Distribution ratios of ethanol were also investigated for tear fluid and blood and as expected the higher water content of tears (~100%) compared with blood (~80%) gave a mean tears-to-blood ratio of 1.25:1 [26,174].

Table 15. Pharmacokinetic parameters (values shown are "mean \pm SD") derived from concentration-time profiles of ethanol in whole blood compared with plasma, urine, and saliva

Parameter	Ethanol dose (0.60 g/kg) ^a		Ethanol dose (0.68 g/kg) ^b		Ethanol dose (0.68 g/kg) ^c	
	Blood	Plasma	Blood	Urine	Blood	Saliva
C_{max} (g/L)	1.08 \pm 0.17	1.20 \pm 0.20	0.92 \pm 0.16	1.08 \pm 0.17	0.91 \pm 0.16	1.09 \pm 0.24
t_{max} (min)	60	60	54	129	38	44
β -slope or k_0 (g/L/h)	0.17 \pm 0.04	0.19 \pm 0.05	0.13 \pm 0.06	0.16 \pm 0.04	0.12 \pm 0.01	0.13 \pm 0.03
C_0 (g/L)	1.02 \pm 0.09	1.12 \pm 0.09	0.98 \pm 0.06	1.40 \pm 0.19	1.0 \pm 0.06	1.1 \pm 0.10
V_d or ρ (L/kg)	0.59 \pm 0.05	0.54 \pm 0.05	0.69 \pm 0.05	0.48 \pm 0.08	0.69 \pm 0.04	0.66 \pm 0.04

^a Alcohol dose administered by intravenous infusion over 60 min ($n = 15$ subjects) [113].

^b Alcohol dose ingested as neat whisky on empty stomach and finished in 20 min ($n = 30$ subjects) [107].

^c Alcohol dose ingested as neat whisky on empty stomach and finished in 20 min ($n = 21$ subjects) [105].

Table 16. Elimination rates of alcohol from breath obtained in experiments with healthy male and female volunteers in three published studies

Gender	n	Elimination rate from breath (mg/L/h)			Breath-alcohol analyzer	Ref.
		Mean	Lowest	Highest		
Male	96	0.080	0.049	0.112	Alcotest 7110 Mk III	[48]
Female	81	0.092	0.065	0.124		
Male	32	0.078	0.048	0.109	Alcotest 7110 Mk III	[206]
Female	27	0.087	0.054	0.120		
Male	9	0.075	0.068	0.083	Intoxilyzer 5000S	[109]
Female	9	0.087	0.070	0.103		

CONCLUDING REMARKS

Much has been learned about the pharmacokinetics of ethanol since the pioneer work began in the 1930s. Quantitative methods for determination of ethanol in blood and other body fluids became available long before such technology was developed for the analysis of other drugs and toxins, which are present in blood at much lower concentration, often 1,000–10,000 times lower than the BAC reached after social drinking. A person's BAC reflects the amount of alcohol that has been absorbed and distributed in the body and using the Widmark formula it is easy to calculate the minimum quantity consumed. During the prosecution of drunken drivers, various questions arise about the ADME of ethanol, often intended to cast doubt on the veracity of the determined BAC. Expert witnesses require a sound knowledge of the pharmacokinetics of ethanol, which is the subject of this forensic science review.

Because ethanol is a legal drug, this makes it a lot easier to recruit healthy volunteers to participate in drinking experiments; however, all human subject testing does require ethical approval. The amounts of ethanol administered are usually fairly low (0.3–1.0 g/kg) to avoid nausea and vomiting, which occurs after larger amounts are consumed quickly on an empty stomach. In most controlled-dosing studies, C_{\max} of the BAC curve falls between 0.8–1.2 g/L, being considerably less than the mean concentrations encountered in forensic casework, such as in apprehended drivers, where the average BAC in most countries is closer to 1.7 g/L [114]. The relationships between BAC, age, and gender of people arrested in Sweden for alcohol-impaired driving are shown in Figure 21 [114].

The relevant scientific literature dealing with human pharmacokinetics of ethanol is spread throughout journals devoted to forensic science and legal medicine as well as clinical pharmacology and substance abuse research. This motivates preparation of comprehensive review articles to bring together this information, making

it more easily accessible to forensic practitioners as exemplified by a recent evidence-based survey of the elimination rates of ethanol from blood [99].

Table 17 summarizes the results from a large number of studies designed to investigate the influence of various factors on ADME of ethanol. Sometimes the results and conclusions from such studies have proven difficult for later investigators to verify. Much seems to depend on the experimental design, the dose of alcohol, the route and timing of administration, and the number of drinking subjects included in the study. Among other things, pharmacokinetic parameters of ethanol should not be derived after very small doses are consumed, because under these circumstances the hepatic enzymes are not necessarily saturated with substrate. Too few blood samples on the postabsorptive phase of the BAC curve are another problem when curve-fitting is done to BAC profiles. The dose of ethanol must be appropriate to ensure that zero-order kinetics operates; otherwise, BAC parameters derived from the postabsorptive portion of the curve are spurious.

The notion of an interaction between drugs used to treat hyperacidity in the stomach, so-called histamine H₂-antagonists (e.g., cimetidine and ranitidine) and ethanol attracted a lot of attention with involvement of pharmaceutical companies. Articles appearing in well-respected

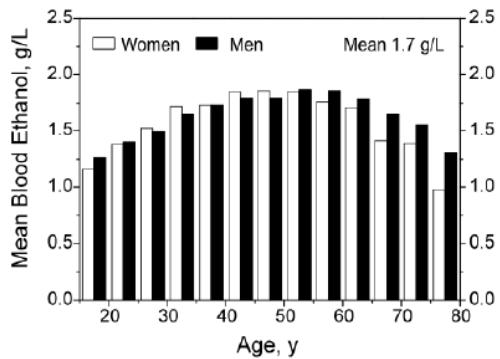


Figure 21. The distribution of blood-alcohol concentrations in men and women apprehended in Sweden for drunken driving in relation to their age. (Combined version of figures appearing in the author's earlier publication [114].)

Table 17. Summary of various factors that might influence absorption, distribution, metabolism, and excretion of ethanol, and comments about the validity of these studies published in peer-reviewed journal articles

Factor investigated	Commentary on the question posed and published findings	Ref.
Phase of the menstrual cycle	Blood-alcohol parameters β and rho were not significantly different during the luteal and the follicular phases of the female monthly cycle as verified by sex steroid hormones estradiol, progesterone, and testosterone in blood.	[36,46,145, 177,195]
Female gender	Less body water per kg body weight in women accounts for the lower V_d in the female gender. Activity of gastric ADH is also lower in women but the role of this enzyme in first-pass metabolism of ethanol is controversial. Nevertheless, the rate of ethanol elimination from blood is slightly faster in women, which seems to be related to a larger liver mass per kg lean body weight.	[45,142, 191,196, 245,260]
Sex steroid hormones	Varying concentrations of testosterone, estradiol, and progesterone in serum from men and women had a small effect on the elimination rate of ethanol from blood. Lower rates were seen in women with lower progesterone levels ($p < 0.05$). Other studies suggest low testosterone levels in men are associated with faster rates of ethanol elimination from blood.	[47,84, 188,189]
Age	During aging body water decreases, which impacts on the volume of distribution of ethanol. A decreased liver and kidney functioning did not slow the elimination rate of ethanol in men over 60 y. The V_d for ethanol was lower in elder men but the rate of elimination of ethanol from blood did not depend on the person's age.	[83,123]
Sobering-up remedies (fructose and glucose)	Administration of carbohydrates, particularly fructose, is considered to accelerate the elimination rate of ethanol from the blood. The type of experimental design, as well as the dose, route and timing of administration of ethanol and sugars, are important for results obtained in such studies. Drinking ethanol mixed with sugars delays gastric emptying and lowers C_{max} . This effect is sometimes confused with faster rate of metabolism.	[17,33,41, 42,180,182 207,219, 235]
Carbonated mixers	Variable effects observed on speed of absorption after drinking highly carbonated drinks; 14 of 21 subjects absorbed faster whereas 7 of 21 absorbed slower or showed no change. Much depends on individual differences in gastric emptying.	[217,274]
Oxygenated drinks	No evidence exists that alcoholic drinks enriched with oxygen result in a faster rate of elimination from blood. A recent study suggested this notion but was criticized for several reasons. On closer examination there was confusion between zero-order and first-order kinetics used to evaluate BAC curves.	[10,87,143, 144]
Kidney dysfunction	Blood-alcohol curves and rate of elimination from blood was the same in patients undergoing hemodialysis compared with age matched men with normal kidney function.	[111]
Liver cirrhosis	Ethanol is metabolized primarily in the liver, so damage to this organ (e.g., hepatitis or necrosis) might be thought to slow the rate of elimination. However, the abundance of hepatic ADH means that even in patients with cirrhosis, some enzyme is still available for the oxidative metabolism of ethanol.	[98,162, 271]
Gastric bypass surgery	Surgery to the gut for obesity leads to a higher C_{max} and earlier t_{max} on the BAC curve. However, the elimination rate of alcohol from blood was not altered after this bypass surgery. By 30–40 min post-dosing, the BAC was the same in operated and nonoperated female subjects and age-matched controls.	[78,139, 272]
Antiulcer drugs	Co-ingestion of cimetidine (Tagamet®) or ranitidine (Zantac®) with ethanol was once claimed to lead to a higher C_{max} on the BAC curve owing to drug-induced inhibition of gastric ADH and amelioration of gastric first-pass metabolism. This conclusion has since been challenged by more recent work. Much depended on administration of too-low doses of alcohol (0.15–0.3 g/kg) and the fed-fasted state of the relatively small number of test subjects.	[24,34,63, 65]

scientific journals suggested that if people on this medication drank alcohol they reached a higher C_{max} and body functioning was more impaired [12,49]. The mechanism proposed to account for the higher C_{max} when alcohol was consumed together with Zantac® or Tagamet® was a drug-induced inhibition of gastric ADH, thus preventing first-pass metabolism of ethanol in the gastric mucosa [27,165,167].

The original studies with these drugs involved only six to eight subjects who consumed small doses of ethanol (0.15–0.3 g/kg) in the morning after eating a fat-rich breakfast [49,67]. Experiments with more volunteer sub-

jects and higher doses of alcohol taken in the morning, at midday, and/or in the evening failed to confirm the original reports [247]. A review of the literature including meta-analysis failed to support the original findings that Zantac® or Tagamet® impacted on the pharmacokinetics of ethanol [62,64,65,259]. Much seemed to depend on the dose of ethanol administered and whether this was consumed on an empty stomach or after a fat-rich meal. Eating a meal before drinking delays gastric emptying and leads to a highly variable absorption rate of ethanol and presentation of substrate to hepatic metabolizing enzymes [63,156,202,249].

The evaluation of bioavailability of a drug by comparing AUC after oral and intravenous administration is not appropriate to drugs metabolized by M-M kinetics, because AUC increases disproportionately with dose and much depends on liver blood flow [44,249]. Moreover, when small doses of ethanol (e.g., 0.15–0.3 g/kg) are consumed with food, the resulting C_{max} is fairly low and small absolute differences in BAC between test and control treatments results in large percentage changes, which are often misleading [65,133,167]. After small doses of ethanol, the BAC curves are highly variable in terms of C_{max} and AUC (Figure 4) and large numbers of drinking subjects are necessary to detect an effect of a particular drug treatment [249].

The general consensus seems to be that cimetidine and ranitidine have a negligible influence on C_{max} of the BAC profiles compared with a placebo or no-drug control treatment [64,247]. The original reports of an adverse interaction between drugs used to treat gastric hyperacidity and the role of age, gender, and drinking habits of the individuals attracted a lot of media attention because the articles were published in high-impact journals [49,67]. When larger doses of alcohol (0.6–0.8 g/kg) were ingested after 1 week of medication with H₂-antagonist drugs, the effects on BAC profiles were small or negligible [63,130].

Another example of questionable results about pharmacokinetics of ethanol concerns alcoholic beverages that are enriched with oxygen, which was claimed led to an increased rate of metabolism and also less pronounced after-effects (hangover) compared with drinking conventional alcoholic beverages [10]. However, a closer examination of the article in question showed confusion between applying first-order or zero-order kinetics to evaluate BAC profiles and the overall results remain highly suspect [10]. Other scientists commented on the study in question and the conflicts that existed with earlier studies of ethanol metabolism after consumption of drinks enriched with oxygen [143,144].

An important forensic aspect about BAC curves is the time required to reach the peak concentration in blood (C_{max}) and the magnitude and duration of the rise in BAC after the last drink [119,125]. Much seems to depend on the pattern of drinking and the amount of alcohol contained in the last drink. In this connection, one needs to distinguish between rapid drinking on an empty stomach and social drinking spread over several hours. After a bolus dose the C_{max} usually occurs on average within 60 min (median) after the end of drinking, but in any individual case this might range from 5 to 120 min [119]. Longer absorption times than 120 min are unlikely unless a pyloric spasm occurred such that absorption took place

primarily through the gastric mucosa and not the upper small intestine [119]. During real-world drinking with repeated intake over several hours, some individuals might have reached their peak BAC before finishing the last drink [277]. Most of the ingested alcohol is absorbed into the bloodstream during the drinking period and only the amount of alcohol contained in the last drink remains to be absorbed.

Table 18 classifies the rates of elimination of alcohol from blood as slow, moderate, rapid, or ultra-rapid in relation to the circumstances under which such rates might be observed in practice. This table also shows the elimination rate of ethanol from the entire body (g/h), which is another important pharmacokinetic parameter, often denoted B_{60} , and is calculated for a man with body weight 70 kg and ethanol distribution volume 0.7 L/kg. The elimination rates given in Table 18 can be considered a physiological range based on several hundred alcohol-dosing studies and a review of the international scientific literature [99]. These rates of alcohol elimination span from a low of 0.10 g/L/h to a high of 0.35 g/L/h, which is a 3.5-fold range. For the vast majority of people, a more practical range of elimination rates for use in forensic casework is 0.10 to 0.25 mg/L/h (2.5-fold range) with 0.15 g/L/h still being a good average value for moderate drinkers.

The elimination rate of alcohol from blood has not been determined in drunken drivers in an unequivocal way—i.e., by measuring the slope of the postabsorptive elimination phase with repetitive blood samples over several hours. Instead, information has been gleaned from double or triple blood samples taken over the space of a few hours from people arrested by the police. If two consecutive blood samples are taken about 60 min apart, the elimination rate of alcohol can be calculated as $(BAC_1 - BAC_2)$ divided by the time difference in hours. This calculation assumes operation of zero-order elimination kinetics and that the person had reached the postabsorptive part of the BAC curve when first and subsequent blood samples were taken [197,226,233].

In a study of alcohol elimination rates in drinking drivers, double blood samples were obtained from 1,090 offenders and the mean rate of elimination of ethanol was 0.19 ± 0.05 g/L/h (\pm SD) with a 95% range from 0.09 to 0.29 g/L/h [110]. In a subsample ($n=21$) of offenders with an abnormally high starting BAC (4.05 g/L), the mean rate of elimination was 0.34 g/L/h (range 0.20 to 0.61 g/L/h) [106]. The reason for a faster elimination rate of alcohol in these individuals probably stems from the fact that in this population there are many chronic drinkers and alcoholics with an enhanced capacity to dispose of ethanol owing to induction of the microsomal CYP2E1 en-

Table 18. Physiological range of elimination rates of ethanol from the blood and from the whole body in humans

Rate of elimination	Blood (g/L/h)	Entire body (g/70 kg/h) ^a	Circumstances or conditions under which such rates might be observed
Slow	0.08–0.10	3.9–4.9	Malnourished individuals or after eating low-protein diets [16] or advanced liver dysfunction (e.g., cirrhosis with portal hypertension). Administration of 4-methyl pyrazole (fomepizole), a drug that blocks the action of the liver enzyme alcohol dehydrogenase [22].
Moderate	0.10–0.15	4.9–7.3	Healthy individuals after drinking moderate amounts of alcohol as a bolus dose on an empty stomach (10-h fast) and reaching BAC of ~1.0 g/L [102].
Rapid	0.15–0.25	7.3–12.3	Regular drinkers, e.g., drinking drivers and nonfasted individuals after drinking moderate doses of ethanol to reach intoxicating BAC [115]. Use of drugs or medications that boost the activity of alcohol oxidative enzymes (e.g., CYP2E1). Intravenous administration of amino acids or carbohydrates, such as fructose, to accelerate oxidative metabolism [171].
Ultra-rapid	0.25–0.35	12.3–17.1	Alcoholics during detoxification or binge drinkers reaching very high BAC >2.0 g/L [18,127] so that CYP2E1 enzyme activity is increased. People with a genetic predisposition for oxidative metabolism of ethanol and other drugs. Conditions that lead to a hypermetabolic state, such as overt stress, drugs (dinitrophenol) or burn trauma [129]

^a Rate of elimination from entire body was calculated for a healthy male subject (70 kg body weight) with a distribution volume of ethanol of 0.7 L/kg.

zyme [137]. The existence of extreme elimination rates (<0.1 g/L and >0.35 g/L) derived from double blood samples are probably artefacts owing to lack of knowledge about the position of the BAC at the time the blood samples were taken.

In most forensic cases only a single blood or breath sample is available for analysis of alcohol, which means that nothing is known about the position of the blood-alcohol curve and the rate at which the individual eliminates alcohol from the bloodstream. During the prosecution of apprehended drivers, the courts might want answers to questions such as:

- How much alcohol was ingested by the suspect to account for the prosecution BAC or BrAC result?
- Does the suspect's statement about his or her drinking agree with the result of the forensic blood- or breath-alcohol analysis?
- What influence, if any, did drinking after driving have on the prosecution BAC or BrAC?
- The suspect claims his or her drink was spiked with vodka; what influence did this have on the prosecution BAC or BrAC?

Questions such as these can be answered without resort to any sophisticated pharmacokinetic software.

Much is already known about the ADME of ethanol, although more studies would be welcomed to characterize BAC curves and pharmacokinetic parameters of etha-

nol under real-world drinking conditions. This might entail the repeated intake of alcoholic beverages (beer, wine, and/or spirits) over several hours to establish C_{max} and t_{max} in relation to the dose and the increases in BAC after the last drink before reaching C_{max} . The article by Zink and Reinhardt [277] was unique in its experimental design of social drinking and this motivated an independent and fresh appraisal of the results and publication in an English language forensic journal [128].

Finally, when blood-alcohol calculations are made in criminal cases, it is important to consider the magnitude of inter- and intraindividual variation in the pharmacokinetic parameters β and rho. These parameters vary between subjects and also within subjects from time to time for the many reasons mentioned and discussed in this review. Blood-alcohol calculations in forensic casework need to be more standardized and, in this connection, the magnitude of uncertainty in the various parameters should be considered and explained when expert statements are made or when testimony is presented in court [23,72].

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APPENDIX

GLOSSARY OF TERMS IN ETHANOL PHARMACOKINETICS

Absorption. Absorption refers to the process by which a drug enters the blood circulation after administration by some extravascular route, such as via the mouth (oral), into a vein (intravenous), intramuscular, subcutaneously, sublingual, or rectally. Absorption therefore represents the uptake of a pharmacological active substance from the site of administration before reaching the systemic circulation.

Absorption deficit. This term, which is often encountered in the older German literature, refers to the fact that the peak blood-alcohol concentration is lower than the value expected for the amount of alcohol consumed, the body weight of the drinker, and volume of distribution of ethanol. The absorption deficit might amount to 10–15% of the dose, which apparently fails to reach the systemic circulation. This means that C_{max} , C_0 , and the area under the curve (AUC) are lower than expected. The absorption deficit is greater if alcohol is consumed together with or after a meal or in repeated doses over several hours as opposed to a bolus dose taken on an empty stomach. One explanation for the “loss of alcohol” is first-pass metabolism in the liver or the gastric mucosa during the absorption process as alcohol enters the systemic circulation. Another mechanism proposed to account for the deficit was binding of some of the ethanol to food components (e.g., amino acids). The bound ethanol was either excreted unchanged or gradually released into the bloodstream over several hours even during the postabsorptive declining portion of the BAC curve.

Absorption half-life. For a drug absorbed by first-order kinetics, the rate of absorption can conveniently be expressed in units of time by calculating the absorption half-life. This is done from C-T data points on the rising phase of the curve before the C_{max} is reached. The absorption rate constant (k_{abs}) has units of reciprocal time (min^{-1} or h^{-1}) and a high k_{abs} (short half-life) means that a drug is absorbed more rapidly with a higher and earlier-occurring C_{max} in the blood. During a time of one half-life, 50% of the drug is absorbed from the site of administration and 90% is absorbed in about four half-lives. Because $t_{1/2} = 0.693/k_{abs}$ the absorption half-life decreases as k_{abs} increases. Pharmacokinetic modeling of the absorption phase of the BAC curve is not easy because the rate of uptake into the blood is much slower from the stomach than the proximal part of the intestine. The absorption rate constant therefore depends on factors influencing gastric emptying. A simple and more pragmatic way is to calculate the ratio of C_{max}/t_{max} having units of g/L/h when rates of absorption are compared for different individuals or test conditions.

Absorption lag-time. For most drugs taken orally a certain time elapses before the active substance is measurable in the systemic circulation. This is known as the lag time and it differs for different drugs depending on, among other things, the dose and dosage form (liquid or solid), pKa of active substance, k_m of hepatic metabolizing enzymes in the liver, extent of first-pass metabolism, and sensitivity of the analytical method used. Because ethanol is in liquid form, absorption into the bloodstream starts immediately and the lag time is therefore negligible.

Area Under the Curve (AUC). AUC refers to area under the concentration-time curve of the drug in blood or some other body fluid. For drugs metabolized by first-order kinetics, the AUC is directly proportional to the dose administered. When bioavailability of a drug after different routes of administration or in different dosage forms is of interest, then AUC is the parameter to measure and compare. However, for drugs metabolized by saturation kinetics (e.g., ethanol, aspirin, GHB, and phenytoin) the AUC increases disproportionately with increase in dose. Under these circumstances bioavailability cannot be calculated by comparing AUC after oral and intravenous administration of the same dose of the drug.

Bioavailability. The word bioavailability is derived from biological and availability and is closely linked to the systemic availability of a drug and thus the fraction of the dose that reaches the systemic circulation. The bioavailability is important for drugs given orally (by mouth) compared with those given by the intravenous route of administration, where bioavailability is 100%. Some formal definitions of bioavailability include:

“Bioavailability is a measure of the rate and extent of absorption of the active form of the drug from its formulation as reflected by the time-concentration curve of the administered drug in the systemic circulation.”

“Bioavailability means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action.”

Biotransformation. This refers to the chemical conversion of a drug into its metabolites by oxidation, reduction, hydrolysis (phase I reactions) or acetylation, and sulfation or glucuronidation (phase II reactions). In general, lipid-soluble drugs are converted into more polar molecules by the action of enzyme-catalyzed biochemical reactions mainly taking place in the liver, all of which facilitates removal by renal excretion.

Body turnover (B_{60}). The elimination rate of ethanol from the entire body expressed per unit of total body mass (g/kg/h) or the entire body weight (g/h). The turnover rate depends on the mass and metabolic capacity of the liver. Turnover is computed from the product of volume of distribution (V_d), in units of L/kg, and the rate of elimination of alcohol from the blood (β) in units of g/L/h. The turnover can also be calculated as dose of alcohol (g/kg) administered divided by the extrapolated time to zero BAC (min_0). A good rule of thumb for turnover rate of ethanol in humans is 0.1 g/kg body weight/h or 7 g/h for a person with a weight of 70 kg. This parameter seems to be independent of gender.

Clinical pharmacology. The word pharmacology comes from the Greek words for drug (*pharmakon*) and discourse (*logos*). Clinical pharmacokinetics is concerned with the safe and effective therapeutic management of a patient with medicines and is tightly linked to the concentrations of drugs determined in blood or plasma in relation to therapeutic efficacy—hence the emergence of therapeutic drug monitoring (TDM) programs.

Compartment modeling. A pharmacokinetic compartment denotes a hypothetical space in the body characterized by a volume and a drug concentration. This compartment forms a part of the overall pharmacokinetic model and is used to account for the observed changes in drug concentration as a function of time. A one-compartment model assumes instantaneous mixing of the administered drug in all body fluids and tissues. A two-compartment model assumes two distinct spaces within the body—a central compartment into which drug initially distributes and a peripheral compartment that reaches equilibrium with the administered drug more slowly.

Diffusion plunge. This refers to the sharp drop in BAC that occurs immediately after reaching C_{max} , as often happens after ethanol is taken as a bolus dose on an empty stomach or after rapid intravenous infusion. During the diffusion plunge, ethanol equilibrates between the blood and the rest of the body water. For some time after reaching C_{max} the concentration of ethanol in the blood is higher than expected for the person's body weight, volume of distribution, and dose administered. Studies have shown that the half-life of the diffusion plunge for ethanol is about 5–10 min.

Disposition. This refers to the sum of all pharmacokinetic processes occurring after a drug reaches the blood circulation, including distribution and elimination (metabolism and excretion) but excluding absorption and other presystemic processes.

Distribution. This refers to the process by which a drug is transported throughout the body after it reaches the bloodstream either by passive diffusion or by active transport from an intravascular space to an extravascular space (body tissue). The drug is distributed into one or more so-called volumes or spaces.

Dosage form. The dosage form of a drug refers to the actual physical form in which the drug is administered or taken by the patient. The dosage form or drug-delivery system might be a liquid, tablet, capsule, coated tablets, spray, or syrup. The particular dosage form of a drug can markedly influence absorption rate of the active substance. In connection with pharmacokinetics of ethanol, the type of alcoholic beverage consumed, whether beer (5% v/v ethanol), wine (12% v/v), spirits (40% v/v), cocktails (15% v/v), or 100% ethanol diluted with water, can be considered the dosage forms. Many alcoholic drinks contain sugars and other constituents that might delay or accelerate the rate of absorption of ethanol into the bloodstream.

Elimination. This is the sum of all processes that remove a drug from the systemic circulation, including metabolic and excretory processes. In the case of ethanol, 90–98% of the dose undergoes metabolism and a maximum of 10% is excreted unchanged in urine, breath, and sweat. After higher doses proportionally more of the drug is eliminated by excretion in breath and urine, because these are first-order rate processes.

Elimination rate constant. For drugs that obey first-order kinetics, the elimination rate constant, k_{el} , is the terminal slope of a log-linear concentration-time curve and is expressed in the units of reciprocal time (h^{-1} or min^{-1}). This stands in contrast to drugs that are eliminated by zero-order kinetics for which the amount removed per unit time is constant and independent of the concentration in the blood. The slope of the pseudolinear phase of the C-T curve for ethanol after intake of a moderate dose is commonly denoted by the Greek letter β or k_o .

Excretion. Excretion refers to the process of removal of a drug and its metabolites from the body with urine, feces, sweat, breath, breast milk, saliva, and bile. Excretion is a first-order process so the relative amounts excreted depend on the dose and the prevailing blood-ethanol concentration. Experimental studies and theoretical calculations show that in the case of ethanol 90–98% of the dose is removed from the body by metabolism and the remaining 2–10% is excreted unchanged, mainly in urine and exhaled air.

First-order kinetics. In a first-order reaction, the change in drug concentration at any time ($-dC/dt$) is proportional to the concentration in blood or plasma at that time. Proportionally more of the drug is eliminated at high concentrations in blood than at low concentrations. The C-T plot for a drug that is metabolized by first-order kinetics is an exponential function when plotted on Cartesian graph paper. The C-T profile becomes a straight line after making a logarithmic transformation. The meaning of k_1 is not easy to conceptualize so elimination rate is mostly expressed as an elimination half-life, which is independent of drug concentration.

First-pass metabolism. First-pass metabolism (FPM) or first-pass effect refers to removal of some fraction of the drug prior to it reaching the systemic circulation. Drugs taken orally might be metabolized by enzymes contained in the gastric mucosa or intestinal lumen, the portal vein, the liver, or the lung. Drugs that undergo an extensive first-pass metabolism have a lower bioavailability and less therapeutic efficacy. Drugs that exhibit a pronounced FPM need to be given by other routes of administered to have any usefulness.

Half-life. The elimination half-life ($t_{1/2}$) of a drug is an important concept in clinical pharmacology because it expresses the rate of change in concentration in blood or plasma in units of time. For drugs that are metabolized by first-order kinetics, the half-life expresses the time required for the concentration of active substance in blood or plasma or amount of drug in the body to decrease by half or 50%. After five half-lives, ~97% of the drug is eliminated from the body. For a drug metabolized according to first-order kinetics, the important relationship $t_{1/2} = 0.693/k_1$ applies, where $0.693 = \ln 2$.

Michaelis-Menten (M-M) kinetics

Leonor Michaelis (1875–1949) and Maud Menten (1879–1960) developed an equation to describe the metabolism of drugs as a capacity-limited process (saturation kinetics), often associated with enzymatic reactions. The parameter V_{max} defines the maximum velocity of the reaction and k_m is the Michaelis constant, which characterizes the affinity of the enzyme for a particular substrate. For ethanol k_m for human liver alcohol dehydrogenase (class I) is about 0.1 g/L and V_{max} is about 0.22 g/L/h.

Overshoot peak. An overshoot peak reflects a situation when the observed C_{max} exceeds the expected C_{max} based on dose of ethanol and time of its occurrence. The magnitude of an overshoot effect (or deficit) is calculated as $(\text{Peak}_{\text{obs}} - \text{Peak}_{\text{exp}})/\text{Peak}_{\text{exp}}$ and is usually expressed as a percentage. An overshoot is sometimes followed by a diffusion plunge, as excess ethanol in the bloodstream equilibrates with the total body water.

Protein binding. This refers to the reversible binding of a drug to serum proteins, mainly albumin, and is an important concept for therapeutic drugs because only the free-fraction (nonbound) is pharmacologically active. An adverse drug-drug interaction might depend on competition between two drugs for binding sites on plasma proteins. Ethanol is generally considered to have negligible protein binding so the concentration in blood and the pharmacological effects are not likely to depend on what drugs might be co-administered or any displacement reaction.

Pharmacokinetics. Some common definitions of the word pharmacokinetics are the following.

"The study of the time course of drugs in biological systems and the mathematical relationships required to develop models to represent the time-dependent changes in the concentrations (or amounts) of drugs in such systems to interpret the data."

"The study of the time course of a drug and metabolite concentration and amounts in biologic fluids, tissue and excreta and the elaboration of suitable models to interpret such data."

"Analysis as a function of time, of all processes which determine the fate of a drug in the body in order to elaborate a model with predictive value."

"The discipline that treats the rate of movement and biotransformation of a drug and its metabolites within the body."

Route of administration. This refers to the way a drug is administered in order to reach the systemic circulation. Depending on the route of administration, the drug has to pass through different biological membranes or barriers to become absorbed. Examples include sublingual (under the tongue), transdermal (through the skin), intranasal, intramuscular, intravenous, intrarterial (into the nose, muscle, vein, or artery), subcutaneous (under the skin), inhalation (via the lungs), enteral (by mouth), or per rectum (via the anus).

Therapeutic drug monitoring. The aim of therapeutic drug monitoring (TDM) is to ensure that the concentration of an active drug in blood or plasma is appropriate for a desired therapeutic effect and without any undesirable side effects or toxicity. The experience gained from TDM allows predictions to be made for effects when the same drug is administered to other patients under the same conditions of dosing. A delicate balance exists between the dose of a drug, the concentration in blood, and the desired therapeutic effect on the individual.

Volume of distribution. The distribution volume of a drug (V_d) is defined as the ratio between the amount of drug in the body (the dose) and the concentration measured in blood or plasma. The V_d does not necessarily represent any particular physiological volume, hence the term “apparent volume of distribution” to describe this important pharmacokinetic parameter. The V_d gives an indication of how the drug is distributed in the various body compartments. Depending on the drug, V_d might vary from a few liters for those that bind to plasma proteins up to several hundred liters for drugs that are highly lipid-soluble and extensively localized in adipose tissue. For ethanol, the V_d is closely related to the proportion of water in the body (~60% for men and ~50% for women) and also water in the blood (~80%).

Zero-order kinetics. Zero-order describes the elimination process when a drug is eliminated at a constant rate independent of concentration in blood or tissues. The elimination rate (dC/dt) is then a fixed amount per unit of time, independent of initial concentration in blood or the amount of drug in the body at that particular time. The units of k_0 or β are g/L/h or g/h. A plot of drug concentration against time gives a straight line with slope $-k_0$ or $-\beta$. A zero-order process is associated with saturation of the metabolic pathway as substrate concentration (BAC) increases up to some threshold value, such as 0.2 g/L in the case of ethanol, which is roughly $(2 \times k_m)$ of the Class I hepatic ADH.



ABOUT THE AUTHOR

A. W. Jones

Alan Wayne Jones was born in Wales but has lived and worked in Sweden for over 30 years. He obtained his B.Sc. and Ph.D. degrees from the University of Wales (Cardiff, U.K.) before starting postdoctoral work at the Karolinska Institutet (Stockholm, Sweden). Dr. Jones is now employed by the Swedish government and works at the Division of Forensic Genetics and Forensic Toxicology at the National Board of Forensic Medicine, in Linköping, south of Stockholm.

Besides his duties in forensic toxicology, Dr. Jones is a guest professor at the University of Health Sciences, also in Linköping. Since receiving his doctorate in 1974, Dr. Jones has worked primarily in the field of biomedical alcohol research and forensic toxicology. He has made extensive studies of the absorption, distribution, and metabolism of ethanol as well as the pharmacology and toxicology of other drugs of abuse. His research has included both human and animal studies, epidemiology of alcohol- and drug-impaired driving, and more recently, interpretative aspects of postmortem toxicology. In 1993 Dr. Jones received a senior doctorate degree (D.Sc.) from the University of Wales for his many contributions to knowledge about the methods of analysis, pharmacology, and toxicology of alcohol and other abused drugs.

Dr. Jones has lectured widely on forensic aspects of alcohol at home and abroad and has testified as an expert witness in the United States, United Kingdom, Denmark, Norway, Ireland, and hundreds of times in Sweden. An experienced peer-reviewer of scientific articles, he serves on the editorial boards of six international journals devoted to biomedical alcohol research, forensic science, analytical toxicology, and legal medicine. He is the author or co-author of more than 360 articles, reviews, and book chapters, most of which have appeared in well-respected scientific journals.

In recognition of his extensive contributions to research and scholarship in the field of alcohol, drugs, and traffic safety, Dr. Jones received the Widmark Award from the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) in 1997. His work in forensic toxicology was recognized in 2002 when he received the Rolla N. Harger Award from the American Academy of Forensic Sciences (AAFS). In 2004 Dr. Jones was a recipient of the Robert F. Borkenstein Award from the U.S. National Safety Council, Committee on Alcohol and Other Drugs.

Alcohol, its absorption, distribution, metabolism, and excretion in the body and pharmacokinetic calculations

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Abstract

The ethanol contained in alcoholic beverages is rapidly absorbed from the gastrointestinal tract and the maximum blood-alcohol concentration (BAC) is usually reached between 10 and 60 min postdosing. Once in the bloodstream, ethanol is distributed into the total body water (TBW) compartment, which comprises ~55–60% of body weight in nonobese males and ~50–55% in females. The volume of distribution (V_d) of ethanol depends on a person's age, gender, and degree of adiposity (ratio of fat to lean tissue). Studies have shown that the average V_d for healthy men and women are ~0.70 and ~0.60 L/kg, respectively. Elimination of ethanol from the body occurs primarily through metabolism (92–98% of dose) by hepatic alcohol dehydrogenase (ADH), an enzyme located in the liver cytosol and a microsomal enzyme, denoted CYP2E1. A small fraction (0.1–0.2%) of the dose of ethanol ingested undergoes nonoxidative metabolism by phase II conjugation reactions leading to formation of ethyl glucuronide and ethyl sulfate. Only between 2 and 10% of the dose of ethanol is excreted unchanged in urine, breath, and in sweat/perspiration. Ethanol exhibits dose-dependent pharmacokinetics, because the hepatic ADH enzyme is saturated with substrate at BAC above 15–20 mg/100 mL (15–20 mg%). Zero-order kinetics operate for most of the postabsorptive elimination phase and the BAC decreases at a constant rate per unit time ranging from 10 to 35 mg% per hour (average 15 mg% per hour for moderate drinkers). Examples of various pharmacokinetic calculations are presented because these are often necessary in forensic science and legal medicine casework.

This article is categorized under:

Toxicology > Alcohol

Toxicology > Analytical Toxicology

Toxicology > Drug-Impaired Driving

KEY WORDS

ADME, ethanol, forensic toxicology, pharmacokinetics, Widmark calculations

1 | INTRODUCTION

The disposition and fate of drugs and other chemical substances in the body began to attract scientific interest and research during the second half of the 19th century coinciding with advances in pharmacy and pharmacology, such as the isolation of

drugs from natural products. This also marked the birth of forensic toxicology and the development of chemical methods to identify poisonous substances in biological specimens, such as in connection with the investigation of sudden, unnatural and/or suspicious deaths (Coley, 1998).

In Victorian Britain, excessive drinking and drunkenness had developed into a major problem for public health and the medical profession was baffled about what happened to alcohol in the body; was it a food, a medicinal drug or a poison? This question was answered in experiments done by Dr. Francis Anstie (1833–1874), who showed that only a small fraction (<10%) of the amount of ethanol ingested (the dose) was excreted unchanged in breath, urine and sweat (Anstie, 1874). It appeared that the bulk of the dose of ethanol was “burnt up” and utilized in the body in the same way as ordinary foodstuffs. Later work by other scientists verified that oxidative metabolism of ethanol produced 7.1 kcal of energy per gram combusted (Lieber, 1994a).

By the 1920s, methods became available for the quantitative analysis of ethanol in small volumes of fingertip blood (~50–100 µL), which permitted making more detailed studies of the absorption, distribution, metabolism, and excretion (ADME) of ethanol in the human body (Widmark, 1922). The physiological laws governing ADME of ethanol were formulated in the 1930s along with the basic principles of ethanol pharmacokinetics (Widmark, 1932).

The blood-alcohol concentration (BAC) reached after a person drinks an alcoholic beverage depends on many factors, including the dose ingested, the type of beverage consumed, the fed-fasted state, the speed of drinking, and the person's body weight, age, and sex (Jones, 2016). Variability in the ADME of ethanol has a profound effect on how a person reacts to the drug, including behavioral and impairment effects (Norberg, Jones, Hahn, & Gabrielsson, 2003). Once absorbed into the bloodstream, ethanol easily passes the blood–brain barrier (BBB) and acts as a depressant of the central nervous system (CNS). The ethanol-induced impairment of body functioning depends on the BAC reached and an important task for forensic practitioners is to interpret analytical results in relation to the observed signs and symptoms of intoxication and drunkenness.

This chapter describes the ADME of ethanol and the many factors influencing the disposition and fate of ethanol in the body. Examples are also given of various pharmacokinetic calculations that might be required in forensic science and legal medicine, such as forward or backward extrapolation of a person's BAC or when alcohol intoxication deaths are investigated.

2 | FORENSIC ASPECTS OF ALCOHOL

The quantitative analysis of ethanol in blood and other biological specimens ranks high among the routine duties of forensic scientists and toxicologists, because abuse of alcohol and drunkenness are underlying factors in many types of crime (Dingwall, 2013). Accurate and precise determination of a person's BAC is relatively simple compared with interpreting the BAC in relation to the quantity of ethanol consumed and the effects on body functioning, including risk of toxicity and poisoning death (Jones, 1991).

Without any doubt, a person's BAC or breath-alcohol concentration (BrAC) is the most important evidence in drink-driving cases, because statutory concentration limits exist in most countries. The alcohol limits currently enforced in England and Wales are 80 mg/100 mL (80 mg%) in blood and 35 µg/100 mL (35 µg%) in breath, whereas in Ireland and Scotland the corresponding limits are 50 mg% BAC and 22 µg% BrAC. The BAC or BrAC give a point estimate of the amount of alcohol in the body at time of sampling, although the police often want to know what the person's BAC was at some earlier time, such as the time of driving or when a crime was committed, such as alleged sexual assault. This requires making a back calculation of a person's BAC, which is often referred to retrograde extrapolation, and requires knowledge of the ADME of ethanol and the factors influencing these processes (Al-Lanqawi et al., 1992; Jackson, Tucker, & Woods, 1991; Montgomery & Reasor, 1992).

BAC calculations are done in slightly different ways depending on the scientific background and training of the expert witness or forensic practitioner and a lot might be gained if these procedures were more standardized (Labay & Logan, 2018). Although there is not yet any international agreement reached, certain guidelines are available, such as those promulgated by the United Kingdom and Ireland Association of Forensic Toxicologists (UKIAFT). This organization has produced a document entitled “alcohol technical defenses,” and this is available on-line via the website (<http://www.ukiaft.co.uk/publications.html>). A lot will depend on the standard of proof necessary, whether beyond a reasonable doubt or the balance of probabilities. Nevertheless, it is crucial that any assumptions made when BAC calculations are done should be fully explained in a deposition or affidavit or during oral testimony in court and therefore subjected to direct and cross-examination (Mason, 1986).

Ethanol is an unusual psychoactive substance in as much that massive amounts must be ingested to bring about its pharmacological effects compared with other recreational drugs. The principal reason for this is that ingested ethanol becomes diluted

with the TBW, which represents 50–60% of body weight. Unlike many other drugs, ethanol does not bind to plasma proteins or other biomolecules, and easily crosses the BBB to cause impairment.

The degree of impairment is dose-dependent; after drinking small doses of ethanol to reach BAC of about 30–50 mg% people become more talkative, they feel less inhibited and experience a mild euphoria. When higher BACs are reached, such as 80–120 mg% the outward signs of impairment are more obvious; reaction times are slower, information processing is more difficult, motor coordination is impaired, and a slurred speech and staggering gait might be seen. Drinking ethanol in the amount necessary to reach BAC of 200 mg% or more is associated with gross intoxication and incapacitation. At BAC > 300 mg% most people would be unresponsive and comatose with risk of dying from paralysis of respiratory centers in the brain stem (Morley, Smith, & Johnson, 2014). Another mechanism of death is asphyxia from inhalation of vomit, which usually occurs at considerably lower BAC than 300 mg%.

Figure 1 shows a schematic diagram illustrating the fate of ethanol in the body resulting in a BAC profile, passage through the BBB, and eliciting pharmacological effects. In the CNS, ethanol molecules interact with cell membranes and receptor proteins, primarily acting as an agonist at the GABA-A receptor and GABAergic neurons are inhibitory, although other receptor sites and mechanisms are involved (Lobo & Harris, 2008). On reaching the CNS, ethanol triggers a cascade of physiological responses depending on the drug dosage, the speed of drinking, and the BAC reached.

3 | BLOOD-ALCOHOL CONCENTRATION

A quantitative dose-effect relationship exists between a person's BAC and the pharmacological effects produced, as reflected in behavioral changes and reduced cognition and impairment of psychomotor performance (Kalant, 1996). The route of administration of ethanol in forensic casework is usually by mouth (peroral), although aqueous solutions can also be given intravenously or rectally leading to inebriation and drunkenness. After rapid drinking on an empty stomach, the BAC is higher and occurs earlier compared with drinking the same dose more slowly over longer times or after eating a meal (Jones & Jonsson, 1994b; Jones, Jonsson, & Neri, 1991).

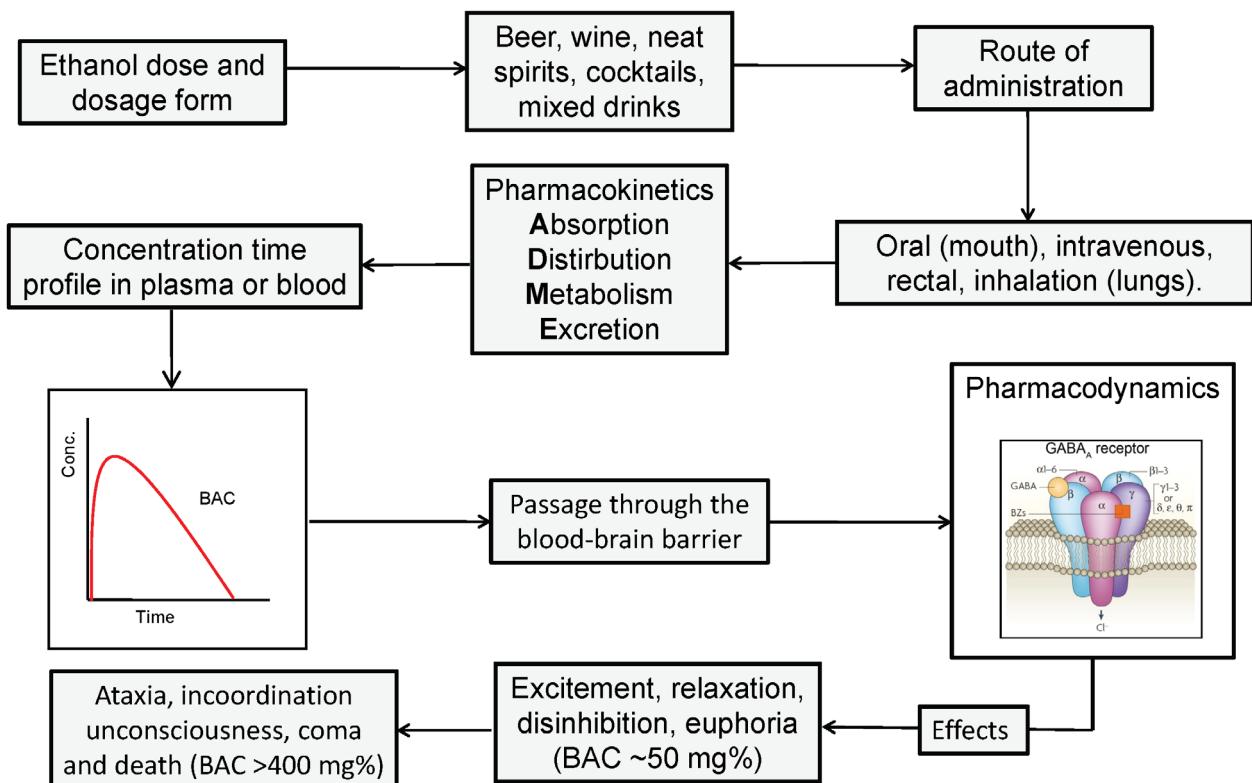


FIGURE 1 Schematic block diagram depicting the disposition and fate of ethanol in the body, resulting in a BAC profile and impacting on cerebral functions causing impairment

3.1 | Endogenous ethanol

Trace amounts of ethanol are produced naturally in the body, by fermentation of carbohydrates in the gut or as a result of biochemical reactions associated with intermediary metabolism, often involving acetaldehyde as a precursor (Ostrovsky, 1986). Sensitive analytical methods reveal that the concentrations of endogenous ethanol in peripheral blood are normally very low of the order of 1 mg/L or 0.001 g/L (0.1 mg%) (Sprung, Bonte, Rudell, Domke, & Frauenrath, 1981; Walker & Curry, 1966). The concentrations of endogenous ethanol in blood are not much different in people with metabolic disturbances, such as Type I diabetes mellitus (Simic, Ajdukovic, Veselinovic, Mitrović, & Djurendic-Brenesel, 2012).

In people suffering from yeast infections in the gastrointestinal tract, such as a proliferation of *Candida albicans*, the concentrations of endogenous ethanol in portal venous blood might be higher than expected, especially after eating carbohydrate-rich meals (Kaji et al., 1984; Logan & Jones, 2000). However, the portal blood has to flow through the liver before reaching the systemic circulation and hepatic alcohol dehydrogenase (ADH) enzymes are effective in clearing low concentrations of ethanol by first-pass metabolism (FPM) (Ammon, Schafer, Hofmann, & Klotz, 1996).

Ethanol is produced endogenously via reduction of acetaldehyde, generated from pyruvate during microbiological and fermentation processes. Many people of Asian descent, such as Chinese and Japanese, lack an effective hepatic low *Km* mitochondrial aldehyde dehydrogenase (ALDH) enzyme, owing to enzyme polymorphism (Agarwal, 2001). Accordingly, these individuals have a deficit capacity to metabolize the acetaldehyde formed during hepatic oxidation of ethanol and concentrations of the toxic metabolite in blood are higher than normal causing adverse effects (Mizoi et al., 1989).

Accordingly, people of Asian decent are more prone to acetaldehyde toxicity than Caucasians and tend to flush in the face after a single drink, they experience nausea, tachycardia, and other unpleasant sensations depending on their ability to metabolize acetaldehyde (Agarwal & Goedde, 1986). This phenomenon is not unlike the reaction caused when a person treated with the alcohol-sensitizing drug disulfiram (Antabuse) drinks alcohol, which works by blocking the action of hepatic ALDH (Kitson, 1977; Koppaka et al., 2012).

4 | ALCOHOLIC BEVERAGES

The three main alcoholic beverages are beers, wines, and spirits, and these differ in the amount of ethanol they contain, which is reflected in their % v/v or % alcohol by volume (ABV). This differs by a factor of about 10 with liquor drinks being 35–45% ABV, table wines 8–12% ABV and beers 3–9% ABV. When forensic BAC calculations are made the % ABV needs to be expressed as % w/v (g/100 mL) so that the number of grams of ethanol consumed and the dose in g/kg body weight can be calculated. Ethanol content in % ABV is converted into percent by weight by multiplying % ABV with the density of ethanol, which is 0.789 g/mL at 20°C.

Table 1 shows the amounts of ethanol contained in beers, wines, and spirits as % ABV and g/100 mL. The number of grams of ethanol consumed will depend on the volume the drink and this might differ between drinking establishments depending on the country (Wansink & van Ittersum, 2005). The notion of a “standard drink” is often discussed but this also differs between countries and in the United States corresponds to 14 g ethanol, whereas in the United Kingdom one unit of alcohol contains 8 g ethanol (Ferner & Chambers, 2001). The last column of Table 1 contains the number of grams of ethanol in one bottle of beer (330 mL), table wine (750 mL), or bottle of liquor (750 mL).

A simple calculation shows that if a person drinks two bottles of 5% ABV beer (2×330 mL) and one bottle of 12% ABV table wine (750 mL), this corresponds to an intake of (2×13 g) or 26 g ethanol from beer and 71 g from wine. This amounts to 97 g of pure ethanol or a dose of 1.21 g/kg for a man weighing 80 kg, which is important information when BAC calculations are made.

5 | FATE OF ALCOHOL IN THE BODY

The BAC reached after drinking an alcoholic beverage depends on an interplay between a number of biochemical and physiological processes, which are discussed in more detail below (see Boxes 1 and 2). Ethanol is one of the few drugs that gets absorbed into the blood through the gastric mucosa, although its rate of uptake into the portal venous blood occurs faster when the stomach contents empty into the duodenum and jejunum.

Factors influencing gastric emptying are therefore important considerations when the rate of absorption and time of reaching peak BAC are considered. In pharmacokinetics, the highest BAC for a given dose is denoted C_{\max} and the time of its occurrence as t_{\max} and these parameters determine the intensity of the pharmacological effects of ethanol ingested. The speed

TABLE 1 Relationships between the alcohol content of different beverages (% v/v or % ABV) and the corresponding weight percent (g/100 mL or % w/v) and the amount of ethanol contained in a typical serving of the drink and in one normal size bottle of the same beverage

Beverage type	Ethanol conc. % ABV ^a	Ethanol conc. in % w/v ^b	Volume (mL) of typical drink ^c	Ethanol (g) per drink	Ethanol (g) in one bottle ^d
Beers	3	2.4	500 ^b	12.0	7.9
	4	3.2		16.0	10.6
	5	4.0		20.0	13.2
	6	4.7		23.5	15.6
Table wines	9	7.1	150	10.6	53.3
	10	7.9		11.9	59.2
	12	9.5		14.2	77.3
Fortified wines (sherry, port)	16	12.6	100	12.6	94.5
	18	14.2		14.2	106.5
	20	15.8		15.8	118.5
Spirits (whisky, gin, vodka, brandy)	35	27.6	25	6.9	201.0
	40	31.6		7.9	231.0
	45	35.6		8.9	267.0

^a% ABV = percentage alcohol by volume.

^b% v/v x 0.79 (density of ethanol) = g% (w/v).

^cIn the United Kingdom, one pint of beer = 568 mL.

^dBeer (330 mL), wine (750 mL), spirits (750 mL).

BOX 1 The pathway of drugs in the body

Absorption. This refers to the uptake of alcohol or other drugs into the bloodstream by different routes of administration, although in forensic casework people drink alcohol, hence absorption takes place from the gastrointestinal tract.

Distribution. Transport of absorbed ethanol with the blood throughout the all body fluids and tissues in proportion to their water content. Rate of equilibration depends on ratio of blood flow to mass of the tissue concerned. Ethanol does not bind to plasma proteins or other biomolecules and easily crosses the blood–brain barrier to cause impairment of brain functioning.

Metabolism. This refers to the breakdown or biotransformation of ethanol into its metabolites (acetaldehyde and acetic acid), by oxidative enzymes mainly located in the liver. Between 90 and 98% of the dose of ethanol ingested is metabolism and the remainder excreted unchanged.

Excretion. The main routes of ethanol excretion are in breath, sweat, and urine, although altogether this amounts of less than 10% of the dose ingested.

Bioavailability. Is defined as the fraction (F) of dose of the drug, often expressed in percent, that reaches the systemic circulation in unchanged form. Bioavailability is 100% when administered by intravenous infusion.

First-pass metabolism. This refers to disposal (metabolism) of some fraction of the dose of an administered drug before it reaches the systemic circulation. For an orally administered drug, this presystemic metabolism occurs by enzymes located in the gut and/or liver.

of drinking and the nature of the drink, such as its ethanol and carbohydrate content, also impact on rate of absorption of ethanol into the bloodstream (Mitchell Jr., Teigen, & Ramchandani, 2014).

During the time ethanol is being consumed and for some time afterwards, absorption is the dominant physiological process and BAC rises until a maximum concentration in blood is reached (C_{max}). The results from many controlled drinking experiments show that C_{max} usually occurs between 10 and 60 min after the end of drinking. But in any individual case t_{max} might

BOX 2 Important elements of drug disposition

Pharmacokinetics. A word derived by combining two Greek words *pharmacon* (drug or poison) and *kinesis* (movement), which entails an evaluation of the concentration-time (C-T) profile of a drug in blood or plasma in mathematical terms.

Pharmacodynamics. Derived from the Greek words *pharmacon* (drug or poison) and *dynamikos* (force or power), and which is concerned with the actions or therapeutic effects of drugs on the body in relation to the dose and route of administration.

Pharmacogenetics. From the Greek word for drug (*pharmacon*) and genetics (origin), a subject that deals role of person's genes and inheritance on drug response. Pharmacogenetics entails studies of racial, ethnic, and genetic factors and how these influence the therapeutic action of drugs including variability in pharmacokinetic and pharmacodynamics response.

Zero-order kinetics. Zero-order kinetics implies that a constant amount of a drug, such as ethanol, is eliminated from the blood (g/L/h) or entire body (g/kg/h) per unit time. The blood-concentration time profile during the elimination phase is linear.

First-order kinetics. For drugs that follow a first-order kinetics, a constant proportion is eliminated from the blood or the entire body per unit time. The higher the concentration (or amount) of drug present the faster is the rate of elimination.

Volume of distribution. Usually denoted V_d refers to a theoretical volume of fluid in which the drug is distributed to give the same concentration as in a reference compartment, usually blood, plasma, or serum. V_d is calculated as ratio of the amount of drug in the body (the dose in g/kg) to the concentration in blood (g/L). V_d is expressed in liters (L) of fluid or L/kg, although these do not correspond to any particular anatomical space in the body.

be as short as 10 min, if gastric emptying is rapid, or as long as 120 min when absorption is slow, such as after a pyloric spasm (Jones, 1991).

Absorption rate of ethanol is a first-order kinetic process, which means its rate is proportional to the concentration or amount of ethanol in the stomach. As the concentration in gastric contents decreases, the rate of absorption slows down and eventually becomes equal to the rate of ethanol metabolism (~10–30 mg% per hour). At this point, the BAC reaches a maximum point and at later times a declining phase starts or there might be a BAC plateau for some time afterwards. Provided no additional ethanol is consumed, the BAC will start to decrease as ethanol is eliminated from the body. Under some circumstances, such as when alcohol is consumed with food, the BAC remains more or less constant (a plateau) for several hours (Jones & Neri, 1991). This signifies that absorption of residual alcohol into the bloodstream is occurring at the same rate as ethanol is being metabolized in the liver, with the result that the BAC remains more or less constant.

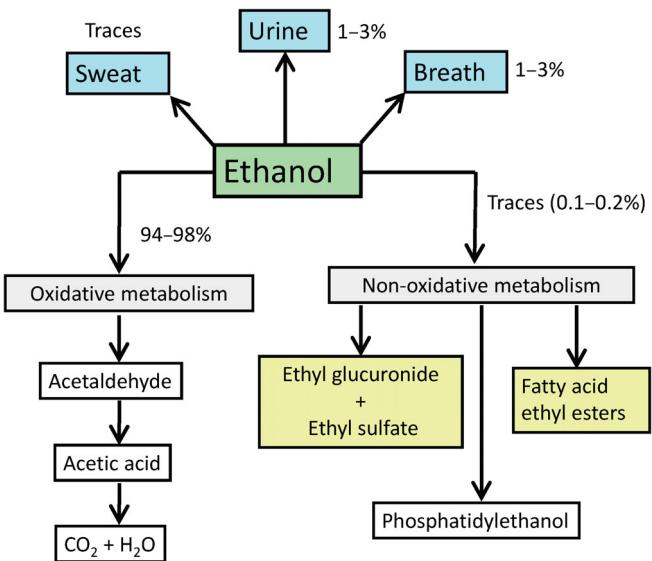
When BAC exceeds 15–20 mg%, the oxidative enzyme mainly responsible for metabolism of ethanol, ADH, is saturated with substrate and is working at its full capacity, hence existence of zero-order kinetics (Wilkinson, 1980). This contrasts with the metabolism and pharmacokinetics of most other drugs, which are eliminated by first-order kinetics. For zero-order processes, the concentration of a substance in blood decreases by a constant amount per unit time, whereas in first-order processes, the rate of decline is proportional to concentration and a constant percentage is eliminated per unit time (Rowland & Tozer, 1995).

Figure 2 illustrates the disposition and fate of ethanol in the body, the relative amounts metabolized, excreted unchanged, and pathways of non-oxidative metabolism.

5.1 | Absorption

Absorption is the process by which a drug passes from the site of administration into the blood stream for transport throughout all body fluids and tissues. Alcohol (ethanol) is a small uncharged molecule that easily crosses biological membranes by passive diffusion process, depending on the concentration gradient (Berggren & Goldberg, 1940). Small amounts of ethanol can be absorbed into the blood through the mucous surfaces of the oral cavity if an alcoholic drink is held in the mouth for sufficiently long time without swallowing any.

FIGURE 2 The metabolism and excretion of ethanol in the body showing the approximate amount eliminated by oxidative and nonoxidative pathways and in the exhaled breath, urine, and sweat



The rate of absorption of ethanol is faster when contents of the stomach enter the duodenum and jejunum, owing to the larger absorption surface area provided by the villi and microvilli of the small intestines. Emptying of the stomach is controlled by the pyloric sphincter, which normally is almost totally closed, owing to tonic contraction of the pyloric muscle. Drinking alcohol together with or after a meal delays gastric emptying and absorption into the blood is slower leading to a lower C_{\max} and a later occurring t_{\max} compared with drinking on an empty stomach (Jones & Jonsson, 1994b). In this connection, the amount of food ingested is seemingly more important than its composition in terms of fat, protein, or carbohydrate content (Jones, Jonsson, & Kechagias, 1997).

In any given individual case, the rate of absorption of ethanol is unpredictable, which makes it difficult to make a definite statement about the C_{\max} and t_{\max} reached after drinking a defined amount of alcohol. However, based on results from hundreds of controlled drinking experiments and evaluation of blood-alcohol curves, some general guidelines can be given as shown in Table 2.

TABLE 2 Some factors influencing the blood-alcohol concentration (BAC) or C_{\max} reached after consumption of a given dose of ethanol and possible mechanism/explanation

Variable or drinking conditions	Possible mechanism and/or explanation	Anticipated effect on the person's BAC
People with low body weight	Less body water	Higher BAC
Appreciable adiposity, high BMI ^a	More fat and less body water	Higher BAC
Female gender	Lower V_d and less body water	Higher BAC
Rapid drinking versus slower ingestion	Faster absorption	Higher BAC
Drinking on empty stomach	Rapid gastric emptying	Higher BAC
Drinking together with or after a meal	Delayed gastric emptying	Lower BAC
High ethanol content in the drinks consumed, for example, spirits versus beer	Faster absorption	Higher BAC
Low or restricted liver blood flow	Slower metabolism	Higher BAC
Smoking cigarettes	Delayed gastric emptying	Lower BAC
Drugs that active pyloric sphincter	Rapid gastric emptying, absorption	Higher BAC
Drugs that delay gastric emptying	Slower absorption	Lower BAC
Gastric bypass surgery	Faster absorption	Higher BAC

^aBMI = body mass index kg/m².

5.2 | Distribution

After its absorption into the portal venous blood, ethanol reaches the liver and passes through the hepatic vein on to the heart, before entering the lungs, passing back to the heart and then being pumped throughout the entire systemic circulation and intra- and extracellular fluids.

The equilibration of ethanol between blood and the extravascular fluids and tissue depends on the cross-sectional area of the local capillary bed and the blood flow per gram of tissue (Kalant, 1996). Organs and tissues with a high rate of blood flow per gram tissue, such as brain, liver, and kidney rapidly equilibrate with the concentration of ethanol in the arterial blood. This contrasts with the bulky skeletal muscles, which take a longer time to equilibrate and during the absorption phase concentrations of ethanol in arterial blood are higher than in venous blood and the difference is especially marked when a bolus dose is ingested on an empty stomach (Jones, Lindberg, & Olsson, 2004).

Ethanol distributes into the total body water (TBW) compartment, which represents between 50 and 60% of body weight or 43–51 L for a person weighing 85 kg (Endres & Gruner, 1994). After ethanol is completely equilibrated in all body fluids and tissues, the concentrations are higher in biofluids with most water, which means sweat, saliva, and urine contain higher concentrations than blood, serum, or plasma (Jones, Hahn, & Stalberg, 1992). Evidence that ethanol distributes into the water compartment of the body comes from experiments in which TBW was determined by isotope dilution using $^2\text{H}_2\text{O}$ and $^3\text{H}_2\text{O}$ and H_2O^{16} as tracers in comparison with ethanol dilution (Endres & Gruner, 1994).

Leaner individuals with heavier body weights have more water to dilute ingested ethanol and therefore they reach a lower BAC compared with lighter individuals after the same dose/kg of ethanol is administered. During aging, especially in men, muscle mass decreases and fatty tissue increases resulting in less TBW per kg of body weight. Accordingly, elderly men >60 years have less TBW to dilute ingested ethanol, which explains why they reach higher BAC for the same ethanol dose per kg ingested compared with younger men (Jones & Neri, 1985).

There are statistically significant differences between men and women in regard to their TBW. Women are generally smaller than men, they are shorter and have lower body weight, and also more fatty tissue. For a water soluble drug like ethanol, its distribution volume (V_d) is influenced by a person's age and gender, with lower values observed in women and in elderly men. Table 3 makes a comparison of ethanol V_d determined for healthy male and female subjects in controlled drinking experiments (Maskell et al., 2019). The average V_d was 0.69 L/kg for men compared with 0.60 L/kg for women, which suggests that after drinking the same dose/kg of ethanol females achieve a roughly 15% higher peak BAC than males.

5.3 | Metabolism

The metabolism of ethanol and other drugs occurs primarily in the liver by the action of various biochemical processes and enzymatic activity (Zakhari, 2006). Unlike other psychoactive drugs, during the metabolism of ethanol energy is produced, actually 7.1 kcal per gram, which is more than that from proteins and carbohydrates (4 kcal/g), but less than from fat catabolism (9 kcal/g) (Lieber, 1991b).

The principal metabolizing enzyme is alcohol dehydrogenase (Class I ADH), which is located in the cytosol fraction of liver cells (hepatocytes) and converts ethanol into acetaldehyde, which is more toxic than the parent drug. Luckily, acetaldehyde is rapidly oxidized further to acetic acid by low k_m ALDH, located in the mitochondria. The acetate produced during the metabolism of ethanol leaves the liver and enters the Krebs cycle and gets converted into CO_2 and H_2O in peripheral organs and tissues (Lieber, 1991a).

During ethanol oxidation by ADH, the coenzyme nicotinamide adenine dinucleotide (NAD^+) is reduced to NADH, which raises the NADH/NAD^+ ratio in hepatocytes. This altered redox state of the liver disturbs other NAD-dependent metabolic reactions. Accordingly, the lactate/pyruvate ratio increases causing a lactic acidosis, which indirectly is responsible for the clinical condition of gout (Lieber, 1997).

TABLE 3 The mean and range of ethanol distribution volumes (Widmark rho-factors) for healthy men and women derived from controlled drinking experiments (Maskell, Jones, Savage, & Scott-Ham, 2019). The mean $\pm SD$ for V_d L/kg and age, body weight, and height of the subjects are shown

Gender	N	Age, years	Weight, kg	Height, cm	Mean V_d or rho-factor, L/kg	Min and max values of V_d or rho-factor
Males	173	33 ± 10.8	75 ± 11.6	177 ± 7.1	0.69 ± 0.086	0.43–0.94
Females	63	35 ± 14.1	64 ± 14.9	164 ± 6.7	0.60 ± 0.100	0.39–0.86

The K_m of the class I isozymes of ADH is only 5–10 mg% for ethanol as substrate, which means that it is saturated at all BAC >15–20 mg% ($2 \times k_m$), hence zero-order kinetics. Another form of the ADH enzyme (class IV) is located in the gastric mucosa and is thought to contribute to first-pass metabolism (FPM) of ethanol causing a reduced bioavailability of the dose (Parlesak, Billinger, Bode, & Bode, 2002). However, there are differences of opinion whether FPM of ethanol is predominantly gastric or hepatic and this question has not been fully resolved (Ramchandani, Bosron, & Li, 2001).

Another hepatic enzyme involved in ethanol metabolism is located in smooth endoplasmic reticulum, particularly the microsomal fraction. Microsomal enzymes constitute a large family of proteins, known as cytochrome P450 monooxygenases, which are responsible for the metabolism of many drugs and xenobiotics, including industrial solvents and pharmaceutical agents (Guengerich, 2006).

The particular form of the P450 enzyme involved in ethanol metabolism to acetaldehyde is denoted CYP2E1, which has a Michaelis constant (K_m) of 60–80 mg/100 mL, being appreciably higher than the K_m of Class I ADH (Tanaka, Terada, & Misawa, 2000). Accordingly, CYP2E1 plays a more important role in the oxidation and clearance of ethanol from the body after heavy drinking when high BACs are reached.



Another property of CYP2E1, besides its higher K_m is the fact that after heavy binge drinking (for weeks or months) enzyme activity increases, making it more effective in oxidative metabolism of ethanol (Tsutsumi, Lasker, Takahashi, & Lieber, 1993). This enzyme induction is the mechanism proposed to explain faster clearance of ethanol from blood in heavy drinkers and alcoholics. However, their enhanced capacity to metabolize ethanol disappears when they stop drinking and remain abstinent for several days (Keiding et al., 1983).

CYP2E1 is also responsible for some undesirable drug-alcohol interactions (Lieber, 1994b), such as with the antipyretic paracetamol (acetaminophen or Tylenol®). This medication is mainly metabolized by conjugation reactions, but a small amount is oxidized by CYP2E1 to highly reactive intermediates. This becomes a clinical problem if and when alcoholics and heavy drinkers have an induced CYP2E1 activity and medicate with paracetamol, which increases the risk for hepatotoxicity and tissue necrosis (Prescott, 2000).

A third liver enzyme system, catalase located within the peroxisomes might theoretically oxidize ethanol at least under *in vitro* conditions. However, its role *in vivo* is questionable, because of the lack of hydrogen peroxide necessary for the reaction to proceed. For all practical purposes, ADH and CYP2E1 are the oxidative enzymes responsible for hepatic metabolism of ethanol in man (Zakhari, 2006).

Figure 3 depicts the oxidative metabolism of ethanol and methanol, which involves the same two hepatic enzymes ADH and ALDH (Roe, 1982). These two aliphatic alcohols compete for binding sites on ADH, which has a higher affinity for ethanol as substrate. Accordingly, at elevated BAC oxidation of methanol is blocked and formation of its toxic metabolites prevented. The first-aid treatment of patients poisoned with methanol is to administer ethanol solutions intravenously to reach

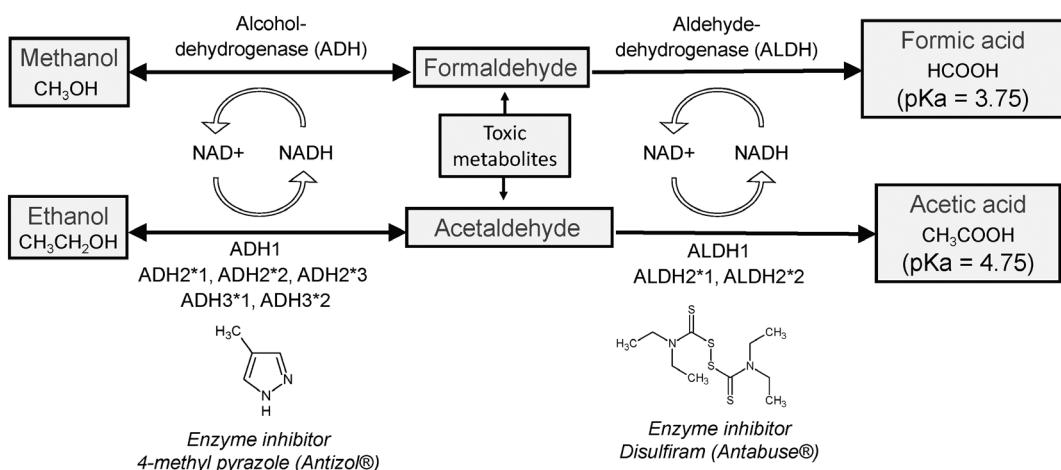


FIGURE 3 Comparison of the metabolism of ethanol and methanol in the liver by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) enzymes into more toxic metabolites, acetaldehyde and formaldehyde. Also shown are the chemical structures of the enzyme inhibitors 4-methyl pyrazole (ADH) and disulfiram (ALDH)

BAC of 100–120 mg% (McMartin, Jacobsen, & Hovda, 2016). After blocking the oxidation by competitive enzyme inhibition, methanol and its toxic metabolites can be removed from the bloodstream by dialysis.

Also shown in Figure 2 are the chemical structure of two enzyme inhibitors, 4-methyl pyrazole (fomepizole or Antizol[®]) in the case of ADH and disulfiram (Antabuse[®]) in the case of ALDH. A metabolic interaction between ethanol and various H₂-antagonist drugs such as cimetidine and ranitidine was suggested when it was found that these substances blocked the activity of ADH located in the gastric mucosa (Lim Jr. et al., 1993). If this happened FPM would be prevented leading to higher BAC than expected after an oral dose, perhaps with clinical and forensic implications. However, research on this topic became highly controversial with proponents for and against there being a significant FPM of ethanol by gastric ADH (Crabb, 1997; Levitt, 1993). Much seemed to depend on the fed-fasted state of the individual and the dose of ethanol ingested, with FPM being more significant after small doses (0.15–0.30 g/kg) and in the postprandial state after breakfast (Oneta et al., 1998). The literature dealing with FPM of ethanol caused by H₂-receptor antagonists was recently reviewed and called for further studies (Moody, 2018).

5.4 | Excretion

Most of the ethanol a person drinks (95–98%) is removed from the body by oxidative metabolism and less than 10% is eliminated unchanged by excretion via the lungs, the kidneys, and skin. After moderate drinking, 2–5% of the dose of ethanol can be recovered by analysis of urine, exhaled air, and sweat. These body fluids are often analyzed in forensic toxicology as proof a person has consumed alcohol in situations when, for some reason, they are required to remain abstinent (Marques & McKnight, 2009). When subjects drank 0.54, 0.68, or 0.85 g/kg as neat whisky, urine samples collected during 7 hr contained 0.70, 0.80, and 1.55% of the dose administered (Jones, 1990). In these experiments, the maximum BAC reached was 120 mg %, so these percentages of the dose excreted are expected to be higher on reaching higher BAC as expected for first-order urinary excretion of ethanol.

5.5 | Nonoxidative metabolites

A small fraction (<0.2%) of the dose of ethanol a person drinks undergoes conjugation reactions in the liver to produce ethyl glucuronide (EtG) and ethyl sulfate (EtS), which are the major nonoxidative metabolites (Palmer, 2009). The pharmacokinetic profiles of EtG and ethanol in blood are different in several respects (Halter, Dresen, Auwaerter, Wurst, & Weinmann, 2008). For example, the EtG curve in blood rises more slowly than the BAC and reaches a peak concentration in blood 1–2 hr later than the ethanol peak. The EtG and ethanol curves are shifted in time and the EtG concentration in blood is about 1,000 times lower than the concentration of ethanol. EtG is also eliminated from the body more slowly and is detectable in blood and urine for several hours longer than ethanol, which means that analysis of EtG is useful to disclose recent drinking in different clinical and forensic situations (Hoiseth et al., 2007).

After gas chromatography-mass spectrometry methods were introduced for analysis of EtG and EtS in blood, urine, and hair strands, a number of forensic applications have emerged (Schmitt, Aderjan, Keller, & Wu, 1995). These metabolites are used as biomarkers for recent drinking and to control abstinence in people expected to refrain from drinking, because of their employment (safety-sensitive work) or participation in treatment programs for alcohol abuse (Walsham & Sherwood, 2012).

In postmortem (PM) toxicology, the analysis of EtG in blood and urine can help in differentiation between ethanol that might be produced after death from antemortem ingestion (Hoiseth et al., 2007). In this connection, there appears to be some advantages of analyzing EtS metabolite as a biomarker of recent drinking and whether postmortem synthesis of ethanol has occurred (Helander & Beck, 2005; Krabseth, Morland, & Hoiseth, 2014). Another method to test the origin of PM ethanol is to determine the ratio of two metabolites of serotonin, the 5-HTOL/5-HIAA ratio as described elsewhere (Helander, Beck, & Jones, 1995).

Other nonoxidative metabolites of ethanol include various fatty acid ethyl esters (FAEE) and phosphatidylethanol (PEth), both of which have found applications in clinical medicine as biomarkers of heavy drinking (Staufer & Yegles, 2016).

6 | PHARMACOKINETIC CALCULATIONS

The two most important pharmacokinetic parameters of ethanol are (a) rate of disappearance from the blood (β -slope) and (b) distribution volume in the body (V_d). The latter is often referred to as the Widmark rho-factor, a term first coined by Erik MP Widmark a pioneer in the development of ethanol pharmacokinetics in the 1930s (Andreasson & Jones, 1996). The rate of

ethanol elimination from blood is derived from the slope of the linear declining phase of the BAC curve in the postabsorptive state when zero-order kinetics operate.

From the results of hundreds of controlled alcohol dosing studies in healthy subjects, average values for the rho-factor or V_d were 0.69 L/kg for men and 0.60 L/kg for women (Maskell et al., 2019). An evidenced-based review of rates of ethanol elimination from blood, showed a range from 10 to 35 mg% per hour (Jones, 2010) with highest rates observed in alcoholics during detoxification and also in some drunken drivers, owing to enzyme induction and contribution of the CYP2E1 pathway.

6.1 | Blood alcohol curves

The fate of ethanol in the body is usually depicted by a graph plotting BAC on the y-axis and time of blood sampling on the x-axis (see Figures 4 and 5). These BAC profiles are evaluated in a quantitative way by defining a set of pharmacokinetic parameters including the β -slope and the volume of distribution (V_d) or rho-factor.

Hundreds of controlled drinking experiments have been published providing a wealth of information about the pharmacokinetics of ethanol and the factors influencing ADME processes (Jones, 2011). The ethanol dose administered in laboratory studies is usually limited to about 1.0 g/kg when this is ingested as a bolus dose on an empty stomach. The consumption of larger doses in a short time on an empty stomach leads to nausea and vomiting.

Administering small doses of ethanol <0.30 g/kg is not recommended because of the relative short duration of the postabsorptive phase. This makes it difficult to calculate the slope of the declining part of the C-T profile in a reliable way.

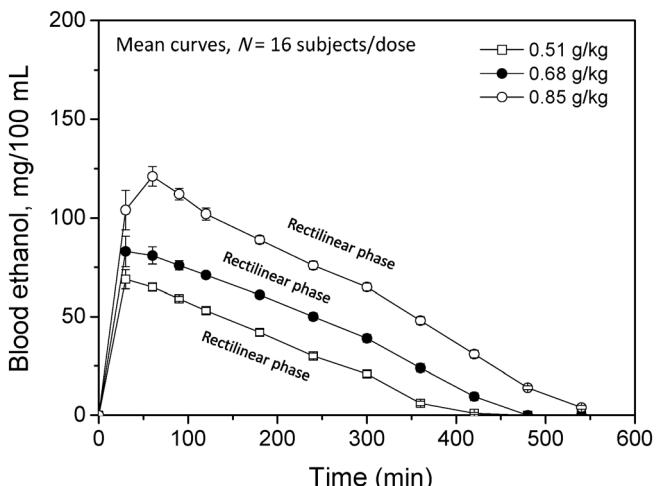


FIGURE 4 Concentration-time profiles of ethanol in blood after three doses of ethanol were consumed on an empty stomach in 15–25 min. Average curves are shown for $N = 16$ subjects ingesting each dose of ethanol.

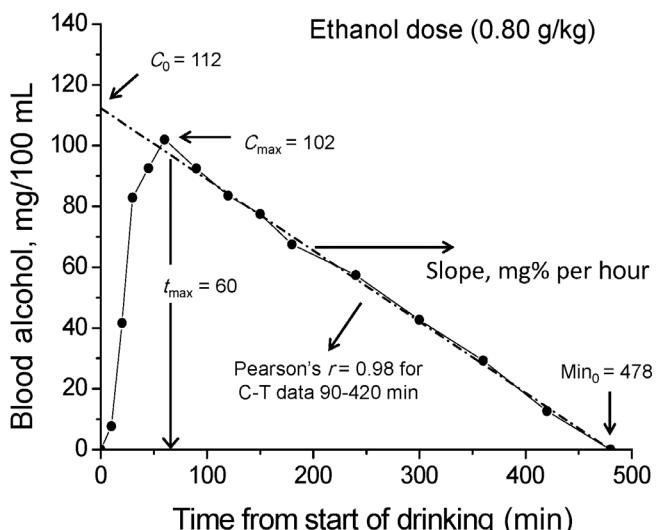


FIGURE 5 Concentration-time profile of ethanol in blood for one subject who drank 0.80 g/kg body weight in 30 min after an overnight fast. The method used to derive the β -slope or zero-order elimination rate is shown as the gradient of the rectilinear descending phase.

Furthermore after drinking such low doses of ethanol, the maximum BAC is insufficient to ensure that ethanol metabolizing enzymes (ADH) are saturated with substrate.

Examples of mean BAC profiles generated in experiments with $N = 16$ subjects after they drank 0.54, 0.68, and 0.85 g/kg ethanol on an empty stomach are shown in Figure 4. Ethanol was consumed as neat whisky in a drinking time of 15–25 min (Jones, 2011). These drinking conditions favor rapid gastric emptying and faster absorption of ethanol into the bloodstream. The rectilinear elimination portions are indicated on the graph and the slopes of these declining phase of the BAC curves represent the rate of elimination from blood.

The C-T profiles shown in Figure 4 share certain characteristics. They begin with a rapid rising portion (absorption) eventually reaching a C_{\max} before this changes to a steady declining phase which shows BAC decreasing at a constant rate per unit time (zero-order kinetics). A linear elimination phase is evident for the three doses of ethanol and this persists for longer after the higher doses of ethanol were consumed.

6.2 | Zero-order kinetics

Figure 5 shows a typical BAC profile from a controlled drinking experiment with a male subject who consumed a dose of 0.80 g/kg ethanol on an empty stomach in 30 min. This C-T plot can be evaluated in a quantitative way by defining certain parameters or summary measures that defines and delineates the shape of the curve (Jones, 1984).

The starting point is to select blood samples on the postabsorptive declining part of the curve and then draw the best fitting straight line through these points. This line is then extrapolated back to intersect the y-axis and forward to intersect the x-axis as shown in Figure 5. The y-intercept corresponds to the parameter C_0 which is the theoretically expected BAC if the dose of ethanol had been absorbed and distributed in all body fluids and tissues without any metabolism occurring. The x-intercept is the time necessary to eliminate alcohol from the bloodstream neglecting the curvilinear part of the curve starting at very low BAC (<5–10 mg%).

The slope of the rectilinear declining phase is calculated as C_0/min_0 or by linear regression analysis of C-T data points to give the rate of elimination of ethanol from blood, which is usually multiplied by 60 to express this rate of decrease in BAC per hour.

The distribution volume (V_d) of ethanol is calculated as the ratio of dose (g/kg) divided by the y-intercept (C_0) shown in Figure 5. The units of V_d are L/kg if BAC is expressed as w/v units (g/L or mg%), otherwise V_d is a dimensionless ratio if mass/mass units (g/kg) are used to report BAC.

Because ethanol absorption occurs from both the stomach and intestine, but at different rates, this makes the mathematical modeling of C-T points on the rising portion of the BAC curve impractical in most cases. A more pragmatic way to determine rate of absorption is simply to divide C_{\max} by the time needed to reach C_{\max} which is usually denoted as t_{\max} expressed in units of mg% per hour. A limitation with this simple method is that blood samples in PK studies are usually taken every 15–30 min so if the peak BAC (C_{\max}) happened to be reached between two sampling times, neither the actual peak value nor its time of occurrence are known with certainty.

Ethanol is cleared from the body at a constant rate per unit time independent of the prevailing BAC as expected for zero-order kinetics ($-dC/dt = k_0$) where k_0 is the zero-order rate constant. This contrasts with the pharmacokinetics of most other drugs, which obey first-order kinetics ($-dC/dt = k_1 C$), and the elimination rate is directly proportional to drug concentration. A constant percentage of the drug is eliminated from the blood per unit time and this is best characterized by its half-life, time necessary to lower the concentration by 50% (Rowland & Tozer, 1995).

6.3 | Applications of the Widmark equation

The zero-order kinetics model for ethanol is appropriate for most of the questions arising in forensic science and legal medicine, although below a BAC of 5–10 mg% the metabolizing enzymes are no longer saturated with substrate and first-order kinetics apply. The shape of the entire postabsorptive phase of the BAC curve therefore looks more like a hockey stick rather than a straight line (see later). In forensic casework, it is rarely necessary to consider BAC under 20 mg% ($2 \times K_m$) when analytical results are interpreted, making it safe to assume zero-order kinetics (Zhang, Wu, & Wan, 2017).

In BAC calculations requested in forensic casework, realistic values for the distribution volume V_d and the rate of elimination rate from blood (β -slope or k_0) are necessary. The person's body weight is given in kg and the amount of ethanol consumed in grams (A), where A/kg is the dose of ethanol and BAC is the concentration in blood in mass/volume units (g/L).

A mathematical equation representing the declining part of the postabsorptive phase of the BAC curve is given by Equation (1):

$$\text{BAC}_t = \text{BAC}_0 - \beta \times t, \quad (1)$$

where BAC_t is the concentration in blood at time t somewhere on the linear declining phase of the curve and BAC_0 is the theoretical concentration in blood extrapolated back to the time of starting to drink (C_0). The linear declining phase has a slope denoted as β or sometimes written as k_0 where the subscript zero indicates zero-order kinetics.

Equation (2) can be rearranged to estimate the BAC existing at an earlier time provided both samples of blood were taken on the postabsorptive portion of the curve:

$$\text{BAC}_1 = \text{BAC}_2 + \beta \times (t_2 - t_1). \quad (2)$$

Similarly, an equation can be derived to calculate how long it takes for a measured BAC to drop below some threshold value, such as 50 mg% as shown in Equation (3).

$$\text{Time (hours)} = [\text{BAC}_t - 50] / \beta, \quad (3)$$

where BAC_t is the measured BAC at time t and β is the elimination rate of ethanol from blood per hour for that person, such as 15 mg% per hour.

The rho-factor or distribution volume of ethanol (V_d) is the concentration of ethanol in the body expressed in relation to some reference compartment, such the bloodstream and is derived from Equations (4a) and (4b) where C_0 is the theoretical BAC extrapolated back to the time of starting to drink, kg is the person's body weight, A is grams of ethanol in all body fluids and [A/kg] is the dose.

$$V_d = (\text{ethanol conc.in body}) / (\text{ethanol conc.in blood}), \quad (4a)$$

$$V_d = \text{dose (A/kg)} / C_0 = A / (\text{kg} \times C_0). \quad (4b)$$

Rearrangement of the above equation gives:

$$A (\text{g}) = C_0 (\text{BAC g/L}) \times \text{body weight (kg)} \times V_d (\text{L/kg}). \quad (5)$$

Equation (5) is often referred to as the Widmark equation and forms the basis of many of the BAC calculations required in forensic casework. Note that if the blood sample was taken too soon after the end of drinking when some of the ingested ethanol was unabsorbed in the stomach, use of Equation (5) would underestimate the amount of ethanol absorbed and distributed in all body fluids.

Equations (1) and (5) are the two basic Widmark equations, and these can be combined in various ways to answer questions arising in forensic science and legal medicine. For example, it might be relevant to calculate a person's BAC a certain number of hours after they started to drink and this can be done using Equation (6).

$$\text{BAC}_t = [A/\text{kg} \times V_d] - (\beta \times t). \quad (6)$$

Here $[A/(\text{kg} \times V_d)]$ is the same as C_0 or the maximum BAC expected for the amount of ethanol consumed and from this is subtracted the ethanol eliminated by metabolism over t hours at a rate of β (mg% per hour or g/L per hour).

This calculation assumes that the entire dose of ethanol (A/kg) reaches the systemic circulation and that FPM is negligible (100% bioavailability). This assumption is tenuous when people consume alcohol in real-world situations, sometimes with a meal and over longer drinking times. If the dose of alcohol was consumed with or after a meal or over several hours, the bioavailability of ethanol might be appreciably less than 100% (Jones & Jonsson, 1994b; Jones, Wigmore, & House, 2006).

If a blood sample is taken on the postabsorptive phase of the BAC curve ($\text{BAC} > 15\text{--}20 \text{ mg\%}$), the result can be used to calculate the total amount of ethanol consumed provided that the time when drinking started is known (Equation (7)). The

oxidative metabolism of ethanol commences immediately after drinking starts, even during the absorption phase. The BAC lost through metabolism is given by the product of $\beta \times t$ where β is the zero-order elimination rate from blood per hour for t hours since drinking started. This amount of ethanol is lost through metabolism and needs to be added to the amount in the body at the time blood was sampled (Equation (7)).

$$\text{Ethanol ingested } A \text{ (gram)} = \text{kg} \times V_d \times (\text{BAC} + \beta \times t). \quad (7)$$

A slight modification to Equation (7) makes it possible to calculate how much ethanol a person would need to drink to reach a certain BAC (e.g., 0.80 g/L or 80 mg%), for example, 5 hr after the start of drinking (Equation (8)).

$$A \text{ (gram)} = \text{kg} \times V_d \times (0.8 + \beta \times 5). \quad (8)$$

The V_d or rho-factor for ethanol depends on the person's age, gender, and degree of adiposity (ratio fat to lean tissue). A simple clinical measure of obesity is given by the person's body mass index (BMI); ratio of weight to height squared (kg/m^2). The Widmark-rho-factor and the person's BMI are negatively correlated as shown in a drinking study in people with widely different BMI (Maudens et al., 2014). A recent evidence-based survey of the distribution volumes of ethanol reported average values of 0.69 L/kg for men and 0.60 L/kg for women as shown in Table 3 (Maskell et al., 2019). In any individual case, the rho-factor might vary by a factor of two in the population of drinkers.

During social drinking, it appears that an appreciable amount of ingested ethanol is oxidized in the gastric mucosa or the liver and does not reach the systemic circulation, owing to a FPM (Jones et al., 2006). FPM is also enhanced if small doses of ethanol (<0.3 g/kg) are ingested in the form of beer (Holford, 1997) or when eating and drinking at the same time, such as during a dinner party or dining out with friends (Jones & Neri, 1991).

6.4 | Ethanol elimination in blood from drunken drivers

The elimination rate of ethanol from blood in apprehended drivers has not been determined in an unequivocal with multiple blood samples taken over several hours on the postabsorptive phase of the BAC curve. However, another approach is to take two consecutive blood samples about 60 min apart and calculate the rate of change in BAC per hour. In this calculation, one needs to assume that zero-order kinetics operate and that the person was in the postabsorptive phase at the time that the first blood sample was taken.

$$\text{Elimination rate} = (\text{BAC}_1 - \text{BAC}_2)/\text{time difference}. \quad (9)$$

Figure 6 shows a frequency distribution of elimination rates of ethanol from blood determined in more than 1,000 apprehended drivers using two consecutive blood samples (Jones & Andersson, 1996). The frequency distribution of β -slopes is a good fit to a Gaussian curve with mean and standard deviation (SD) of $19 \pm 5 \text{ mg\% per hour}$ and median and 95% range

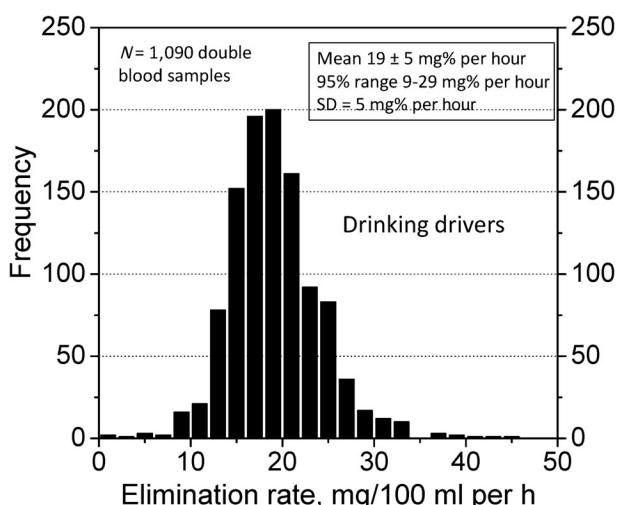


FIGURE 6 Frequency distribution of the rates of ethanol elimination from blood in apprehended drunken drivers in Sweden. These results were derived from the change in BAC between two blood samples taken about 60 min apart. Values under 10 mg% per hour probably reflect those drivers who were not on the post-peak phase when the first blood sample was taken

of 19 mg% per hour and 11 and 31 mg% per hour, respectively. Values less than 10 mg% per hour are unrealistic and probably represent cases where the suspect had consumed alcohol fairly recently and was not in the postabsorption phase when the first blood sample was taken (Neuteboom & Jones, 1990).

Table 4 shows results from an evidence-based survey of ethanol elimination rates from blood based on a review of hundreds of published studies available in the literature (Jones, 2010). These articles were selected if they met certain criteria with regard to experimental design, such as rapid drinking on an empty stomach, moderate ethanol dose, and adequate number of blood samples taken on the postabsorptive phase to allow pharmacokinetic evaluation. The values of the β -factor in Table 4 can be considered representative for the general population of healthy individuals. Also shown are the amounts of ethanol cleared from the whole body for a man with rho-factor 0.70 L/kg and a body weight 70 kg. The experimental conditions or circumstances that might explain the various rates of ethanol elimination are considered.

In apprehended drivers (Figure 6), the average elimination rate of ethanol from blood was 19 mg% per hour, which is slightly higher than 15 mg% per hour observed in moderate drinkers (Hoiseth, Wiik, Kristoffersen, & Morland, 2016). The difference stems from an over-representation of heavy drinkers and alcoholics in the population of drunken drivers, the latter being individuals with an enhanced capacity to metabolize alcohol, via the CYP2E1 pathway (Keiding et al., 1983).

Racial and ethnic differences in rates of ethanol elimination are small compared with many other factors, although there is evidence that people of Asian descent, owing to a polymorphism in the Class I hepatic ADH enzyme, have a slightly faster rate of metabolism (Mizoi et al., 1989). The slope of the declining phase of the BAC curve was slightly steeper in Japanese subjects after drinking the same dose as Caucasians (Mizoi et al., 1987). Enzyme polymorphism of Class I ADH explains why East Asians have a more active β -2 ADH isoenzyme and a higher V_{max} for ethanol as its substrate (Crabb, Bosron, & Li, 1987). Nevertheless, there is a considerable overlap in the elimination rates in Asians, Caucasians and African Americans, so the racial differences lack any forensic significance (Li et al., 2000).

6.5 | Updating the Widmark equation

In 1981, investigators from New Zealand published a paper calling for an update of the Widmark equation, especially the rho-factor or volume of distribution (Watson, Watson, & Batt, 1981). They felt that because Widmark's pharmacokinetic studies were done in the 1930s, in only 20 men and 10 women an update was warranted considering the lasting importance of the work. They further pointed out that body composition had changed a lot since the 1930s, with much more obesity evident in today's society (Yanovski & Yanovski, 2002).

Watson et al. (1981) advocated that it would be better to calculate an individual rho-factor based on anthropometric data, such as age, height, weight, and degree of adiposity for that particular individual. They presented multiple regression equations with TBW as the dependent variable and age (year), weight (kg) the height (cm) as the independent variables. These

TABLE 4 Physiological range of elimination rates of ethanol from blood (mg% per hour) in healthy subjects according to an evidence-based review of the literature (Jones, 2010). Also shown are elimination rates from whole body (g/hr) along with circumstances or conditions under which these might be obtained

Elimination rate from blood, mg% per hour	Elimination rate from whole body, g/hr ^a	Conditions, treatment, or the special circumstances when such elimination rates are encountered
8–10	4–5	People with liver dysfunction (e.g., owing to cirrhosis or carcinoma) or who might be malnourished or eat low-protein diets. Treatment with enzyme inhibitor of alcohol dehydrogenase, fomepizole (4-methyl pyrazole).
10–12	5–6	Consumption of moderate doses of alcohol by healthy individuals after an overnight (10 hr) fast.
12–16	6–8	Consumption of moderate doses of ethanol under nonfasting conditions.
16–25	8–12	Healthy individuals who consumed alcohol to reach intoxicating BAC (>120 mg%) such as is the case with drunken drivers
25–35	12–17	Alcoholics during detoxification or periods of heavy drinking for days or weeks to reach high BAC (>200 mg%). People having a genetic predisposition for rapid disposal of ethanol. Factors leading to a hypermetabolic state (e.g., after burn trauma or hyperthyroidism or certain medicinal drugs).

^aThis calculation assumes a nonobese male person with body weight 70 kg and volume of distribution (rho-factor) of ethanol of 0.70 L/kg.

Equations (10) and (11) were derived from TBW measurements in liters (L) determined by isotope dilution experiments in hundreds of people.

$$\begin{aligned} \text{TBW Liters (men)} &= 2.447 - 0.09516 \text{ age (year)} + 0.1074 \text{ height (cm)} + 0.3362 \text{ weight (kg)} \\ \text{Residual standard deviation} &= 3.78 \text{ L} \end{aligned} \quad (10)$$

$$\begin{aligned} \text{TBW Liters (women)} &= -2.097 + 0.1069 \text{ height (cm)} + 0.2466 \text{ weight (kg)} \\ \text{Residual standard deviation} &= 3.60 \text{ L} \end{aligned} \quad (11)$$

Once TBW is calculated from Equations (10) or (11), the rho-factor is obtained as the ratio of the percentage of water in body (L/kg) and percentage of water in the blood in g/100 mL.

$$\text{Rho-factor} = \text{water in body (L/kg)} / \text{water in blood (g/100 mL)}. \quad (12)$$

The water content of blood is fairly constant in healthy individuals (78–82% w/w), although the values are slightly higher in females, owing to their lower hematocrit and thus a greater plasma fraction per unit volume (Lenter, 1981). Accurate determination of the water content of biological specimens is done by desiccation (de Jong et al., 1987). A multicenter study in Germany determined the water content of blood from 682 men and 141 women. The water content was 78.2% w/w (range 74.8–83.3) for men and 79.4% w/w (range 76.3–82.5) for women, a small but statistically significant gender difference (Iffland, West, Bilzer, & Schuff, 1999). Note that these percentages are weight/weight, because the aliquots of blood and serum were weighed before desiccation. Because density of whole blood is 1.055 g/mL (Lenter, 1981) percentages of water in blood on the basis of weight/volume are 82.5% w/v for men and 83.8% w/v for women (% w/w × 1.055).

Use of Equation (10) assuming a 45-year-old man with a body weight of 85 kg and height 184 cm gives a TBW value of 46.5 L or 54.7% of body weight. If the water content of whole blood is taken as 83 g/100 mL, the ratio of TBW (%) to blood water (%) is 0.66 L/kg (54.7%/83% = 0.66 L/g), which is a rho-factor tailored for this individual.

The residual SD in the above equations reveals the uncertainty in calculating TBW; 95% of individuals fall within $\pm 2 \times SD$, which is 40 ± 7.6 L (18.9%) for a man with TBW of 40 L.

Another approach to updating the Widmark equation, that received certain currency, was suggested by Forrest (1986). His method for estimating V_d or rho-factor depended on calculating the person's BMI as ratio of weight (kg) to height in meters squared (kg/m^2) and considering the percentage fat-free body mass (Barbour, 2001).

6.6 | Saturation kinetics

If the C-T profile of ethanol in the postabsorptive state is followed from high to low BAC, its shape is more like a hockey stick as depicted in Figure 7 (left graph). Accordingly, when BAC is about twice the K_m of ADH, the enzymatic reaction works at its maximum velocity (V_{max}). In the case of ethanol, the postabsorptive elimination phase is linear down to a BAC of 15–20 mg% but thereafter starts to tail off and under 10 mg% follows an exponential function (Holford, 1987). Making a logarithmic transformation of the BAC data produces the curve shown in Figure 7 (right part). The transformed data (semi-log plot) indicates that first-order kinetics operates at BAC of <15 mg% and that clearance of ethanol can be described by its elimination half-life of about 15–20 min (Ludden, 1991).

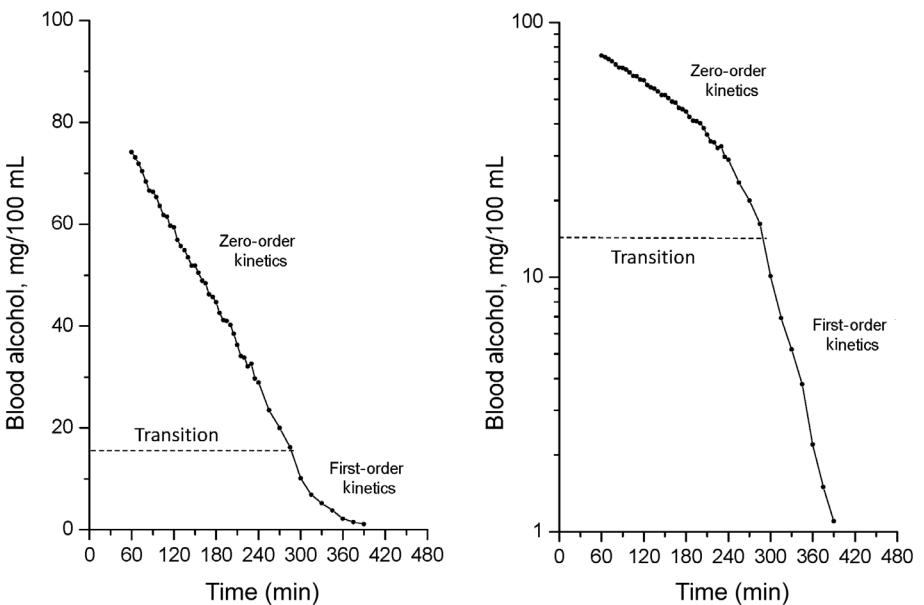
In mathematical terms, the BAC extending from high to low concentration can be fitted to the Michaelis–Menten Equation (13), which was developed many years ago to characterize the rate of enzymatic reactions (Lundquist & Wolthers, 1958; Wagner, 1973).

$$(-dC/dt) = (V_{max} \times \text{BAC}) / (K_m + \text{BAC}). \quad (13)$$

The two important kinetic parameters are K_m , which is the Michaelis constant denoting the binding power of the enzyme to its substrate and the other is V_{max} which is the maximum velocity of the biochemical reaction.

With reference to Equation (13), when the BAC (substrate concentration) is considerably higher than K_m (0.05–0.1 g/L of ADH), the equation simplifies to Equation (14), which conforms to a zero-order rate constant (V_{max}) (Wagner, Wilkinson, & Ganes, 1989).

FIGURE 7 Concentration-time profiles of ethanol in blood with samples taken at 5 min intervals from high to low ethanol concentrations. The left plot on Cartesian coordinates shows the hockey stick shape characteristic of drugs with saturation kinetics. The right plot shows a logarithmic transformation of the BAC measurements and existence of zero-order kinetics (BAC > 20 mg%) and first-order kinetics (BAC < 15–20 mg %)



$$(-dC/dt) = V_{\max} = k_0. \quad (14)$$

On the other hand when the BAC is much less than K_m , Equation (13) simplifies to Equation (15), which is the formula for a first-order kinetic reaction, with a rate in direct proportion to the substrate concentration (BAC). The first-order rate constant (k_1) is given by the ratio V_{\max}/K_m in Equation (16).

$$(-dC/dt) = (V_{\max}/K_m) \times BAC, \quad (15)$$

$$(-dC/dt) = k_1 \times BAC. \quad (16)$$

Figure 7 (right part) shows a logarithmic transformation of the same C-T data for ethanol elimination and one notices that at concentrations 15 mg%, a straight line is evident and can be used to derive the half-life ($t^{1/2}$) from the first-order rate constant (k_1) as $\ln 2/k_1$ or $t^{1/2} = 0.693/k_1$. This half-life was determined to be 15–20 min, so after five half-lives or 75–100 min, the BAC would have decreased to reach the endogenous levels.

7 | FORENSIC APPLICATIONS

There are numerous applications of the Widmark equation in forensic casework when alcohol-related crimes, such as drunken driving, are investigated (Gullberg, 2007). Such calculations are done somewhat differently depending on the traditions and case law existing in various countries and whether metric units or imperial units are used in the calculations for things like body weight, height, volume of drink, and concentration units for reporting BAC (Gullberg, 2007). Much can be said for trying to standardize the way various BAC calculations are made, including retrograde extrapolation (Brick, 2006; LaBay & Logan, 2018).

7.1 | Amount of alcohol in body

The average BAC in apprehended drunken drivers in most countries is between 1.5 and 1.8 g/L (150–180 mg/100 mL) and are easy to convert into the amount of ethanol absorbed and distributed in all body fluids at time of sampling blood. For a male subject with body weight 80 kg, volume of distribution 0.7 L/kg and BAC of 150 or 180 mg% (1.5 or 1.8 g/L), there are 84 g or 100.8 g of ethanol equilibrated throughout all body fluids and tissues. Table 5 presents further examples of this calculation based on BACs from 50 to 450 g/L for men with body weights of 60, 80, or 100 kg.

The amount of ethanol in grams is easy to convert into volumes of different alcoholic drinks based on the information contained in Table 1. For example, 100.8 g ethanol is contained in 325 mL of whisky or vodka (40% v/v). If there was any

alcohol remaining unabsorbed in the stomach when blood was sampled, this would not be reflected in the amount of alcohol in the body calculated from the BAC.

7.2 | Total amount of alcohol consumed

The metabolism of ethanol starts as soon as alcohol reaches the stomach and passes through the liver so some part of the amount ingested has been disposed of by the time a blood sample is taken in forensic casework (Wagner, Wilkinson, & Ganes, 1990). If the number of hours elapsed between start of drinking and the time of sampling blood is known then it is easy to calculate the total amount of ethanol consumed. This calculation can be done in two ways (a) assuming an average elimination rate from blood (β) of $0.15 \text{ g L}^{-1} \text{ hr}^{-1}$ (15 mg% per hour) or elimination from the whole body at a rate of $0.10 \text{ g kg}^{-1} \text{ hr}^{-1}$, the latter being the product of $\beta \times \rho$.

Equation (17) uses the elimination rate from blood along with average values of β and rho-factors and the BAC at t hours from start of drinking.

TABLE 5 Relationship between blood alcohol concentration (BAC) and amount of ethanol consumed

Blood alcohol conc. mg%	Body weight, kg ^a	Ethanol (g) in whole body	Metabolism (g) over time of 3 hr ^b	Amount of ethanol consumed (g) ^c
50	60	21.1	6	27.1
	80	28.2	8	36.2
	100	35.2	10	45.2
80	60	33.8	6	39.8
	80	45.0	8	53.0
	100	56.3	10	63.3
100	60	42.2	6	48.2
	80	56.3	8	64.3
	100	70.4	10	80.4
150	60	63.4	6	69.4
	80	84.5	8	92.5
	100	105.6	10	115.6
200	60	84.5	6	90.5
	80	112.6	8	120.6
	100	140.8	10	150.8
250	60	105.6	6	111.6
	80	140.8	8	148.8
	100	176.0	10	186.0
350	60	126.2	6	132.2
	80	169.0	8	177.0
	100	246.4	10	256.4
450	60	190.1	6	196.1
	80	253.5	8	261.8
	100	316.9	10	326.9

Note: The calculations assume body weights of 60, 80, or 100 kg and a time of 3 hr from start of drinking to time of sampling blood. The elimination rate of ethanol from whole blood is assumed to be $0.10 \text{ g kg}^{-1} \text{ hr}^{-1}$.

^aThe calculations assumed a healthy male subject with Widmark rho-factor (V_d) of 0.70 L/kg.

^bEthanol is metabolized at a rate of 0.1 g ethanol per kg body weight per hour from the start of drinking.

^cThe sum of alcohol in body and the amount metabolized over 3 hr.

$$\text{Total amount consumed (g)} = [\text{kg} \times \text{rho} (\text{BAC}_t + \beta \times t)]. \quad (17)$$

From the results of hundreds of controlled drinking experiments, it has been shown that the elimination rate of ethanol from the whole body is approximately 0.1 g ethanol per kg body weight per hour or 7 g/hr for a 70 kg person and 9 g/hr for a person weighing 90 kg. Equation (18) shows an alternative way of calculating the total amount of alcohol a person has consumed from the measured BAC and when t hours have elapsed since the start of drinking.

$$\text{Total amount consumed (g)} = [(\text{BAC} \times \text{kg} \times \text{rho}) + (0.1 \times \text{kg} \times t)]. \quad (18)$$

Consider a man with a body weight of 80 kg, a rho-factor of 0.70 L/Kg and BAC determined 5 hr after the start of drinking or 2 hr after end of drinking. Use of Equation (17) and assuming a BAC of 100 mg% (1.0 g/L) shows that the total amount of ethanol consumed was 98 g ethanol whereas use of Equation (18) gives a result of 96 g ethanol. The blood sample was taken 2 hr after the end of drinking, which makes it safe to assume that absorption and distribution of ethanol in all body fluids was complete.

7.3 | Alcohol poisoning death

Deaths attributed to acute alcohol poisoning are often encountered during forensic investigations (Darde, Duflou, Torok, & Prolov, 2013; Jones, Kugelberg, Holmgren, & Ahlner, 2011). A recent report from the UK National Health Service reported that there were 5,507 alcohol-specific deaths in 2016, being up by 4% compared with 2015 and 11% up compared with 2006 (NHS_UK, 2018). Assuming that the autopsy BAC is the same as it was in the body at the time of death, the result can be used to calculate the amount of alcohol the deceased had consumed prior to death.

In this calculation, consider that a man (body weight 73 kg) was found dead at his home and the autopsy BAC was reported as 389 mg% (femoral blood), which is consistent with an acute poisoning death. Because this was a sudden and unexpected death an inquest was held in the coroner's court and the question arose about how much alcohol the deceased had consumed?

From interviews with friends, it emerged that the day prior to death the man started drinking at a pub at 12 noon and continued the whole day. Time of death, according to the pathologists report, was 2:00 a.m., the following morning. Accordingly, 14 hr elapsed from time of starting to drink alcohol and the time of death, when metabolism of ethanol ceases. Over these 14 hr, the man eliminates ~ 102 g ethanol from the body ($14 \times 7.3 = 102$ g) through metabolism. The autopsy BAC of 389 mg% corresponds to there being 198 g ethanol absorbed and distributed in all body fluids at time of death (assuming a rho-factor 0.70 L/kg).

The deceased had therefore consumed 300 g ethanol ($102\text{ g} + 198\text{ g} = 300\text{ g}$) some time before death, which is roughly the amount contained in 4.2 bottles (750 mL each) of wine (12% ABV) or 949 mL spirits (40% ABV) or 7.6 L of beer (5% ABV), by any standards a heavy drinking binge (Jones & Holmgren, 2009).

7.4 | Retrograde extrapolation

The concentration of ethanol determined in blood gives useful information about the amount of alcohol in the body and the degree of impairment at the time blood was sampled. However, the police are often more interested in knowing what the person's BAC was at an earlier time, such as the time an alcohol-related crime was committed (Jackson et al., 1991; Lewis, 1987).

Typically, a person might be involved in a traffic crash and rushed to hospital for medical treatment so blood for toxicology was taken several hours after the time of the traffic incident. Accordingly, the result of analysis is not a reliable indication of the driver's BAC at the time of the crash (Lewis, 1986).

Because ethanol is eliminated from the blood at a constant rate per unit time (zero-order kinetics), making a forward or backward calculation of the BAC is valid provided the postabsorptive phase existed at the material times (Stowell & Stowell, 1998). Another necessary assumption is that there was no consumption of alcohol after the time of driving and before the blood was taken for toxicological analysis. Most people eliminate alcohol from the blood at a rate of 10–20 mg% per hour with a mean of 15 mg% per hour for moderate drinkers. The mean elimination rate in people arrested for drunken driving is slightly higher closer to 19 mg% per hour, because there are many heavy drinkers in this population (Jones & Andersson, 1996).

Examples of back calculating BAC starting from 20 mg% to times of 2–8 hr before the blood sample was taken are shown in Table 6. The mean (range) of ethanol elimination rates were 15 mg% per hour (10–20 mg% per hour), which are appropriate for most healthy people with normal liver function. Performing a back calculation of BAC in drink-driving cases is a contentious issue, because a person might be below a statutory limit initially but above the limit after the back-calculation was done (Lewis, 1987). To avoid having to perform back calculation routinely, the law in some jurisdictions presumes that if blood was sampled within 2 hr of driving, the analytical result would be considered not less than the BAC existing at the time of driving. In other jurisdiction, no time restrictions apply and the prosecution BAC is that which was determined at the time of sampling.

When sexual assault crimes are investigated, the victims might not report an offense until many hours afterwards. Blood samples for determination of ethanol are obtained when the victims are eventually examined by medical professionals. Under these circumstances, the BAC and state of inebriation are different than they were when the alleged crime took place (Jones, Kugelberg, Holmgren, & Ahlner, 2008). If a victim of date rape had zero, BAC detected a back calculation is not possible, but if the analytical result is >15–20 mg%, then such a calculation is certainly possible.

In sexual assault cases, there is no need to consider a threshold BAC, such as the statutory alcohol limit for driving. So in a back-calculation it is better to use an average elimination rate of ethanol from blood for that particular individual. If a young lady with little or no experience of drinking alcohol was sexually assaulted, then 15 mg% per hour is a good rate of elimination to use. Assuming the measured BAC was 120 mg% at the time of sampling blood and the crime occurred 6 hr earlier, with reasonable scientific certainty the victim's was ~210 mg% [120 + (6 × 15) = 210 mg%].

If the subject in the above example was accustomed to drinking alcohol, a more appropriate elimination rate would be 19 mg% per hour, which was the median value in drinking drivers (Jones & Andersson, 1996). The estimated BAC would then be closer to 234 mg% [120 + (6 × 19) = 234 mg%]. In such cases, a perpetrator often maintains that sexual activity was consensual, and a key question that arises in litigation and expert witness testimony is whether the victim, because of drink, drugs, or a medical condition, was so incapacitated that they could not possibly have consented to sex (Gunby, Carline, Bellis, & Beynon, 2012).

7.5 | Forward extrapolation

In some forensic cases, a blood sample might be unavailable, but the suspect or witnesses provided information about the amount of alcohol consumed. This information along with the person's age, body weight, and gender can be used to calculate the BAC expected. Assume a man with body weight 80 kg (rho-factor of 0.70 g/L) who drank five bottles of 5% ABV beer (360 mL per bottle) in 1 hr. The expert witness might be asked to calculate the likely BAC 2 hr after the end of drinking or 3 hr after start of drinking.

TABLE 6 Blood-alcohol concentrations calculated at the time of an offense derived from a BAC of 20 mg% at the time of sampling, which was assumed to be 2–8 hr later. The calculation assumes zero-order kinetics and mean and range of ethanol elimination rates 15 mg% (10 to 20 mg% per hour)

Hours elapsed after the traffic offence ^a	Estimated BAC at time of offense (mean value) ^b	Spread of estimated BAC		
		Lowest	Highest	Highest minus lowest BAC
2	50	40	60	20
3	65	50	80	30
4	80	60	100	40
5	95	70	120	50
6	110	80	140	60
7	125	90	160	70
8	140	100	180	80

^a Assumes an analytical result of 20 mg% BAC after making a deduction for uncertainty.

^b The calculation assumes that the suspect had reached the postpeak phase of the BAC curve at time of offense and that no further alcohol was consumed before blood was taken for toxicology.

One bottle of beer contains 14.2 g ethanol, so five bottles contain 71.1 g. According to Equation (5), the maximum BAC for this amount of ethanol is 127 mg% if absorption and distribution in all body fluids occurred instantaneously. During the 1 hr drinking and 2 hr postdrinking, the BAC can drop by ~45 mg% ($3 \times 15 \text{ mg\% per hour}$) through metabolism, so the BAC 2 hr after drinking ends is likely to be about 82 mg% ($127 - 45 = 82$). This calculation assumes that bioavailability of the dose of ethanol in the five beers was 100% so 82 mg% is the highest possible result. After drinking beer as described in this example, bioavailability of ethanol is less than 100%, owing to carbohydrate content of the beer, dilution factors, time elements, and FPM (Holford, 1997).

In UK law, it is an offense for a person to be in charge of a motor vehicle with a BAC above the statutory limit of 80 mg%. Sometimes a person is found asleep in the vehicle but claims they had no intention of driving until the next morning when the BAC would be below the statutory limit for driving. If the BAC at the time of arrest is known, this allows calculating the time necessary for the concentration to decrease below a certain threshold value, such as 20 mg% as shown in Table 7.

In the calculation, the starting BAC was assumed to range from 50 to 300 mg% and the mean and (range) of ethanol elimination rates from blood were taken as 15 mg% per hour (10–20 mg% per hour) assuming zero-order kinetics above 20 mg% BAC. In reality, it is virtually impossible for a person to know what their BAC was a certain time after drinking, without making an analytical determination. Neither does a person know their rate of ethanol metabolism, which varies as much between as within the same individual on different occasions (Jones & Jonsson, 1994a).

Furthermore, after a few hours of sleep, the subjective feelings of intoxication are less evident, because the brain has adapted to the ethanol environment, a phenomenon known as acute tolerance (Kalant, 1998). This apparent sobering-up effect and greater impairment observed on the rising limb of the BAC curve compared with the postabsorptive phase have been demonstrated experimentally and were recently reviewed (Holland & Ferner, 2017; Martin & Moss, 1993).

Another need to make a forward projection of BAC arises when a driver is arrested for driving under the influence of alcohol and after obtaining a blood sample for forensic analysis the person is released from custody. Five hours later the same person was seen by the police driving again, but on this second occasion, blood was not available for analysis of alcohol. The prosecution might wonder what the suspect's BAC was on this second occasion, so that this information could be made part of the prosecution case. Table 7 can help to answer this question and the example assumes a statutory BAC limit for driving of 20 mg%.

A good rule of thumb for ethanol elimination rate from the whole body is 0.10 g/kg body weight per hour or 9 g ethanol per hour for man weighing 90 kg. Accordingly, if this person drank a whole bottle of 12% ABV wine (750 mL), this would correspond to 71.1 g ethanol and would require a time of ~7.9 hr ($71.1/9 = 7.9 \text{ hr}$) to be disposed of by the body. If instead the person weighed only 60 kg, it would require 11.9 hr to become alcohol-free ($71.1/6 = 11.9 \text{ hr}$).

8 | CONCLUDING REMARKS

Interpreting the concentration of ethanol and/or other drugs in biological specimens is an important duty for forensic practitioners, such as when alcohol-related crimes are investigated, including drinking and driving, drug-facilitated sexual assault, and violent behavior in general (Jones, 2017). Alcohol is the psychoactive substance most often encountered in forensic casework, because heavy drinking and drunkenness are tightly linked to deviant behavior and criminal activity (Fairbairn et al., 2017).

TABLE 7 Estimated times necessary for a measured blood-alcohol concentration (BAC) to decrease below 20 mg/100 mL assuming that zero-order kinetics of ethanol operate

Starting BAC, mg%	Mean time (hours) to 20 mg% BAC ^a	Range of times (hours) to 20 mg% BAC ^b
50	2.0	1.2–3.0
100	5.3	3.2–8.0
150	8.7	5.2–13.0
200	12.0	7.2–18.0
300	18.7	11.2–28.0

^aBased on an average elimination rate from blood of 15 mg/100 mL per hour.

^bBased on minimum and maximum elimination rates from blood of 10–25 mg/100 mL per hour.

The BACs reached after drinking depend on the dose administered and interaction between the various ADME processes (Jones & Jonsson, 1994a). People react differently to the same dose of alcohol, which is coupled to individual, genetic and environmental factors, and intersubject variations in ADME. Also important is the development of tolerance to ethanol's impairment effects as well as cultural and/or social norms that determine a person's drinking habits. It is the concentration of ethanol in arterial blood reaching the brain that causes impairment of body functions. However, in forensic science practice venous blood is the specimen submitted for toxicological analysis. The concentration of ethanol in breath follows more closely the arterial BAC, which suggests that BrAC is a better indicator of brain exposure to alcohol than venous BAC as demonstrated in a controlled alcohol dosing study (Lindberg et al., 2007). The magnitude of arterio–venous differences in ethanol concentration is more pronounced on the absorption phase of the BAC curve compared with the postabsorptive declining phase (Jones et al., 2004).

Overconsumption of alcohol and drunkenness is responsible for many unnatural deaths, including suicides, accidental drownings, acute poisonings, and damage to body organ and tissue after years of heavy drinking (Jones & Holmgren, 2003; Koski, Ojanpera, & Vuori, 2002). The BAC determined at autopsy can be converted into the amount of ethanol in the body at the time of death. Death from acute ethanol poisoning might occur with a BAC in the range from 300 to 400 mg%, although there are many exceptions. The mechanism of death from acute alcohol poisoning is by paralysis of the respiratory centers in the brain stem—hence a type of drug-induced asphyxia (Heatley & Crane, 1990). The frequency distribution of BAC in acute poisoning deaths overlaps with the BAC observed in people arrested for drunken driving (Jones & Holmgren, 2003). However, the mean BAC in fatalities is ~200 mg% higher than in drunken drivers, which are in the range 150–180 mg% in most countries indicating many binge drinkers among these traffic delinquents.

The present article has reviewed key aspects of ethanol's ADME and gives examples of various pharmacokinetic calculations that might be required in forensic science casework, such as drink-driving prosecutions. The evidence for prosecution of traffic offenders in most countries is nowadays obtained by analysis of ethanol in expired air with various types of evidential breath-alcohol analyzer (Dubowski, 1991). Scores of studies show that BAC and BrAC are highly correlated over a wide range of concentrations so it is perfectly feasible that pharmacokinetic calculations are done using BrAC measures and the resulting breath-ethanol profiles (Jones, 2011). One study showed that the V_d of ethanol derived from analysis of breath alcohol curves in male and female subjects, assuming a 2,100:1 blood-breath ratio, agreed well with values expected from analysis of blood samples (Cowan Jr., Weathermon, McCutcheon, & Oliver, 1996). However, more studies are needed in which ADME of ethanol was characterized from BrAC profiles and pharmacokinetic parameters derived and compared with conventional BAC analysis (Dettling, Witte, Skopp, Graw, & Haffner, 2009).

Forensic alcohol research is broadly multidisciplinary and the relevant scientific literature is spread throughout many different scientific journals, book chapters, and review articles (Jones, 2008, 2011). The scientific basis of the various BAC calculations has high validity, because hundreds of human ethanol dosing studies have been done since the 1930s (Holford, 1987; Widmark, 1932). The relevant pharmacokinetic parameters of ethanol, such as V_d and rate of elimination from blood (β -slope), are well-defined in men and women including magnitude of inter- and intrasubject variations (Jones, 2010; Maskell et al., 2019).

Hopefully, this review will serve as a primer for use by forensic scientists and others when they are required to interpret BAC measurements in alcohol-related cases, write expert statements or appear in court and testify as expert witnesses.

CONFLICT OF INTEREST

The author has declared no conflicts of interest in publishing this article.

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Idiographically Determined Versus Standard Absorption Periods in Alcohol Administration Studies

Rebecca L. Schacht, Susan A. Stoner, William H. George, and Jeanette Norris

Background: Effects of alcohol vary depending on blood alcohol level and limb. Some researchers use standard absorption periods (SAPs) to determine when postdrinking experimental protocols should begin. Others use an idiographically determined absorption period (IDAP) based on criterion breath alcohol concentration (BrAC). We investigated and compared the characteristics of each method.

Methods: Sixty-eight social drinkers (47% women) consumed a bolus dose of alcohol intended to raise BrAC to 0.08%. BrACs were recorded every 3 minutes until beginning to descend. Minutes to reach criterion BrAC (0.06%) and between-subjects postdrinking BrAC variability were analyzed.

Results: Mean time to reach 0.06% BrAC was 22.9 ± 14.6 minutes. Standard deviations in BrAC were 4 times greater using SAPs compared to IDAPs. Ten percent of participants' BrAC readings were on the descending limb 30 minutes postdrinking, and 25% were descending at 45 minutes postdrinking.

Conclusions: IDAPs result in less BrAC variability and may reduce experimental noise relative to SAPs. Experimental control in future alcohol administration studies may be enhanced by the use of IDAPs instead of SAPs.

Key Words: Alcohol Administration, Absorption Period.

THE EFFECTS OF alcohol vary with both blood alcohol level and limb of the blood alcohol curve. Although individual differences exist (e.g., Holdstock and de Wit, 1998; King et al., 2002), the ascending limb is associated with euphoria and stimulation, whereas the descending limb is associated with dysphoria and sedation (e.g., Martin et al., 1993). Therefore, in studies examining physiological effects of alcohol, it is important to establish both alcohol level and limb.

Many laboratories use a standard absorption period (SAP), e.g., 30 minutes, to allow a bolus dose of alcohol to be absorbed and participants to arrive at the desired breath alcohol concentration (BrAC) before beginning the experimental protocol. Shorter SAPs are used to place participants on the ascending limb, whereas longer SAPs are used to place participants on the descending limb (e.g., Schweizer et al., 2006). The SAP method may result in large variability in BrACs, and in some cases variability in BrAC limb, during completion of dependent measures. An alternative method is to use idiographically determined absorption periods (IDAPs)—that

is, those based on participant's individual BrAC readings—to determine BrAC level and limb. In this approach, participants are breathalyzed at regular intervals until their BrACs reach a criterion and they begin dependent measures (e.g., Giancola and Zeichner, 1997). IDAPs would seem to provide better experimental control than SAPs with regards to both BrAC level and limb, but to our knowledge, this has not been demonstrated empirically. Furthermore, given the labor intensive nature of using IDAPs with repeated breath analysis, the question of to what, if any, extent the method is worth using is in need of investigation.

The purpose of the present study is to describe and compare the characteristics of these 2 experimental methods for allowing for alcohol absorption. We expected less heterogeneity in participants' BrACs using IDAPs compared to SAPs. Moreover, we expected that heterogeneity of BrACs would increase as the length of the SAPs increased.

MATERIAL AND METHODS

Participants ($N = 68$; 47% women) were aged 21 to 35 ($M = 25.0$, $SD = 3.4$) and reported consuming between 1 and 35 alcoholic beverages per week. All participants provided informed consent before participating, and all procedures were approved by the university's Institutional Review Board. Participants were 78% European American, 7% Asian, 6% Latino/a, 3% African American, and 6% multi-racial or other. Collins and colleagues' (1985) Daily Drinking Calendar was used to assess typical weekly alcohol consumption. Men's mean reported number of drinks per week was 11.0 ($SD = 9.1$), whereas women's was 7.4 ($SD = 7.1$). Participants were instructed not to consume food or caloric drinks for 4 hours before their scheduled appointment. They were asked to confirm that they had adhered to these instructions when they arrived at the

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laboratory. They were given 9 minutes to consume an oral bolus dose based on body weight of 100-proof vodka mixed with orange juice intended to achieve a peak BrAC of 0.08% (0.82 g/kg for men, 0.69 g/kg for women). Beverages were divided into 3 cups containing roughly equal portions, and participants were instructed to finish 1 cup every 3 minutes. BrAC was tested every 3 minutes using an Intoxilyzer 5000 (CMI Inc., Owensboro, KY). Subjective intoxication was measured by asking participants "On a scale of 1 (no effect) to 10 (extremely intoxicated), how intoxicated do you feel right now?" each time they were breathalyzed. Participants rinsed their mouths with water 5 times and were breathalyzed until at least 3 consecutive descending readings below peak BrAC were obtained. Participants were debriefed, paid \$15/h, and released when BrAC dropped to 0.03%. Participants' BrACs were analyzed to determine whether BrAC patterns would differ based on whether an SAP or an IDAP was used.

RESULTS

Analyses were conducted using Statistical Package for the Social Sciences, version 15 (SPSS Inc., Chicago, IL). A hypothetical criterion of 0.06% BrAC was set as the point at which ascending-limb participants would move on to dependent measures. This was chosen as an IDAP/SAP comparison point because it has been used in the past to ensure that participants were on the ascending limb of intoxication while completing dependent measures (e.g., Davis et al., 2009; George et al., 2009). Participants were classified as having met criterion if they had 2 ascending BrAC readings at 0.06 or above. Descriptive statistics are in Table 1. Participants took a mean of 65.2 minutes postdrinking to reach their highest BrAC reading ($SD = 28.8$, minimum = 23 min, maximum = 161 min). Using an IDAP, the mean ($\pm SD$) time to reach criterion (0.06% BrAC) was 22.9 ± 14.6 minutes. IDAPs ranged from 6.0 to 76.0 minutes (Fig. 1). SAP SDs were approximately 4 times greater than was the IDAP SD (Fig. 1). To evaluate whether variability in IDAP BrAC remained low after subjects reached criterion BrAC,

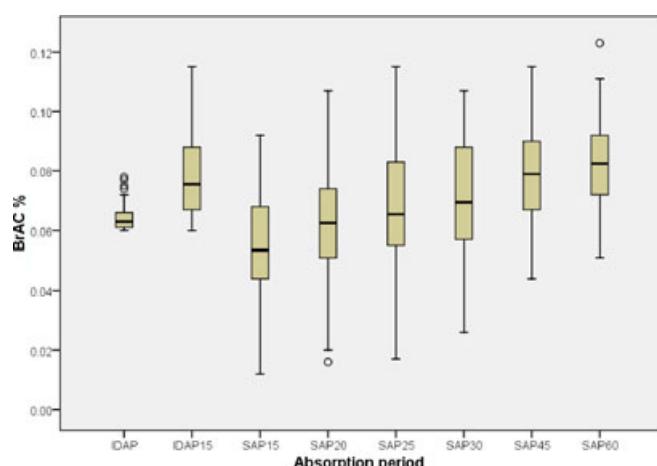


Fig. 1. Box plot showing the variability resulting from varying hypothetical idiographically determined versus standard absorption periods. IDAP, idiographically determined absorption period (criterion BrAC = 0.06%); IDAP15, IDAP + 15 minutes; SAPx, standard absorption period of x minutes. Median values denoted by horizontal line in each box. Whiskers indicate minimum and maximum values. Box lengths indicate interquartile range. Circles indicate outliers (>1.5 interquartiles away from the box).

we analyzed BrAC readings using IDAP at 15 minutes postcriterion (IDAP + 15) and found a mean of 0.078 ± 0.012 , slightly over one-half the SD associated with SAPs. At 15 minutes postdrinking, 0% of participants had reached peak BrAC. At 30, 45, and 60 minutes postdrinking, 10.4% ($n = 7$), 25.4% ($n = 17$), and 52.2% ($n = 35$), respectively, of participants' BrAC had peaked or begun descending.

DISCUSSION

These findings suggest that, compared to IDAPs, using SAPs to determine when participants should begin experimental protocols introduces a significant amount of variance in subjects' BrACs and may result in the misclassification of BrAC limb, especially as SAPs increase. Comparatively lower variance associated with IDAPs persisted over time. Fifteen minutes after reaching criterion BrAC, the standard deviation in subjects' BrACs remained below the standard deviations associated with SAPs, implying that subjects completing dependent measures immediately postcriterion BrAC would continue to maintain similar BrACs. In addition, a notable minority (10%) of participants were already on the descending limb 30 minutes postdrinking. Subjective ratings of intoxication did not appear to vary significantly depending on absorption period protocol; however, this may be because of the range (1 to 10) of the data, which was limited in comparison with BrAC readings.

Variability in subjective intoxication did not differ significantly depending on whether an idiographic or SAP was used. Although many researchers use BrACs instead of subjective intoxication as their primary measure of intoxication, the importance of subjective intoxication, controlling for BrAC, in predicting postdrinking perceptions, performance, behaviors, and other outcomes remains open to investigation.

Table 1. Descriptive Statistics for Breath Alcohol Concentrations (BrACs) and Subjective Intoxication Ratings Achieved Using Hypothetical Waiting Periods

	M	SD	Min	Max
Peak	0.091	0.013	0.055	0.123
IDAP	0.065	0.005	0.060	0.082
SI	5.4	1.8	2.0	9.0
IDAP + 15	0.078	0.012	0.060	0.120
SI	6.6	2.1	2.0	10.0
SAP15	0.056	0.018	0.012	0.095
SI	5.0	1.9	1.0	9.0
SAP20	0.064	0.020	0.016	0.107
SI	5.5	2.0	1.0	10.0
SAP25	0.067	0.019	0.017	0.115
SI	6.1	2.0	1.0	10.0
SAP30	0.072	0.018	0.026	0.107
SI	6.3	2.0	1.0	10.0

IDAP, idiographically determined absorption period based on a criterion BrAC of 0.06%; Peak, mean highest BrAC reading; SAPx, standard absorption period of x minutes; SI, subjective intoxication rated on a 1 to 10 scale and assessed concurrently with BrAC.

Because the present study examined subjective intoxication and BrAC as dependent variables, rather than as independent variables predicting some outcome, it cannot speak to the relative importance of subjective versus objective measures of intoxication.

Maintaining homogeneity of participant limb when assessing dependent measures is crucial in light of research indicating that subjective effects and behavior differ with regard to whether an individual's BrAC is on the ascent or has peaked and begun falling. For example, individuals on the ascending limb of intoxication exhibit more aggressive behavior than those on with similar BrACs on the descending limb (Giancola and Zeichner, 1997). These effects have been observed in a range of dependent measures, including those relating to motor skills, cognition, and sexuality (Holdstock and de Wit, 1998; Schweizer et al., 2006). Thus, reducing the variance in BrAC may decrease the likelihood of Type II errors, as variability in other dependent measures is likely to decrease if methods ensure that participants complete them on the same limb.

The primary compromise in using IDAPs is increased variance in postdrinking time before dependent measures. This potential threat to internal validity can be eliminated by using yoked control subjects (e.g., Giancola and Zeichner, 1997), such that each no-alcohol subject is assigned to undergo the same waiting period and number of breath tests as a corresponding alcohol subject. Further research should include direct comparisons of behavioral-dependent measures based on whether idiographically determined or SAPs are used and assess whether subjective or objective measures of intoxication differ in their capacity to predict behavior across the biphasic curve of intoxication. However, the current findings indicate that use of IDAPs reduces BrAC variance and ensures that BrAC limb is accurately identified.

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Absorption and Peak Blood Alcohol Concentration After Drinking Beer, Wine, or Spirits

Mack C. Mitchell Jr., Erin L. Teigen, and Vijay A. Ramchandani

Background: Both the amount and the rate of absorption of ethanol (EtOH) from alcoholic beverages are key determinants of the peak blood alcohol concentration (BAC) and exposure of organs other than gut and liver. Previous studies suggest EtOH is absorbed more rapidly in the fasting than in the postprandial state. The concentration of EtOH and the type of beverage may determine gastric emptying/absorption of EtOH.

Methods: The pharmacokinetics of EtOH were measured in 15 healthy men after consumption of 0.5 g of EtOH/kg body weight. During this 3-session crossover study, subjects consumed in separate sessions, beer (5.1% v/v), white wine (12.5% v/v), or vodka/tonic (20% v/v) over 20 minutes following an overnight fast. BAC was measured by gas chromatography at multiple points after consumption.

Results: Peak BAC (C_{max}) was significantly higher ($p < 0.001$) after vodka/tonic (77.4 ± 17.0 mg/dl) than after wine (61.7 ± 10.8 mg/dl) or beer (50.3 ± 9.8 mg/dl) and was significantly higher ($p < 0.001$) after wine than beer. The time to C_{max} occurred significantly earlier ($p < 0.01$) after vodka/tonic (36 ± 10 minutes) compared to wine (54 ± 14 minutes) or beer (62 ± 23 minutes). Six subjects exceeded a C_{max} of 80 mg/dl after vodka/tonic, but none exceeded this limit after beer or wine. The area under the concentration-time curve (AUC) was significantly greater after drinking vodka/tonic ($p < 0.001$) than after wine or beer. Comparison of AUCs indicated the relative bioavailability of EtOH was lower after drinking beer.

Conclusions: Findings indicate that BAC is higher after drinking vodka/tonic than beer or wine after fasting. A binge pattern is significantly more likely to result in BAC above 80 mg/dl after drinking vodka/tonic than beer or wine. Men drinking on an empty stomach should know BAC will vary depending on beverage type and the rate and amount of EtOH.

Key Words: Alcohol Absorption, Pharmacokinetics, Beverage Type Differences, Blood Alcohol Concentrations, Gastric Emptying Rate.

BECAUSE THE RATE of absorption of ethanol (EtOH) is greater than its rate of elimination, both the amount of EtOH consumed and the rate of absorption of alcoholic beverages are key determinants of the peak blood alcohol concentration (BAC) (Holt, 1981; Ramchandani et al., 2001a; Wilkinson et al., 1977). The rate of

elimination of EtOH is determined largely by the activity of hepatic alcohol dehydrogenases (ADH), the primary enzymes that metabolize EtOH. ADH are saturated at relatively low concentrations of EtOH leading to a rate of elimination that is sometimes described as zero-order kinetics at higher concentrations and pseudo-linear or first-order at concentrations below the saturation of ADH (Wilkinson et al., 1977). Absorption of EtOH continues over a prolonged period of time after ingesting alcoholic beverages, with BACs continuing to increase until the rate of elimination exceeds the rate of absorption. For these reasons, the rate of absorption is a primary determinant of the peak BAC. As most of the effects of EtOH are related to the BAC, variables that influence the rate of absorption are of interest. EtOH is absorbed more rapidly during the fasting than the fed state (DiPadova et al., 1987; Horowitz et al., 1989; Jones, 2000; Roine et al., 1993). Furthermore, solid meals delay gastric emptying more so than liquid meals, and the rate of absorption of EtOH consumed with a solid meal is likewise slower than when consumed with a liquid meal, probably as a function of the rate of gastric emptying (Horowitz et al., 1989). Other studies indicate that food increases the rate of elimination of EtOH (Ramchandani et al., 2001b).

During both the fasting and fed states, the rate of absorption of alcoholic beverages is influenced by the

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concentration of EtOH in the beverage (Mellanby, 1919; Roine et al., 1993; Wilkinson et al., 1977). Previous studies reported variable results depending on the concentration of alcohol in the beverage. Some studies reported that higher concentration of alcohol in a beverage delays the rate of gastric emptying particularly after a meal (Haggard et al., 1941; Roine et al., 1991; Sedman et al., 1976). Many of these studies utilized 95% EtOH diluted to different concentrations in orange juice or water, although some used beer, wine, and spirits (both diluted and neat) during or after a standard meal. Other studies have reported that during the fasting state, dilute alcoholic beverages such as beer are absorbed more slowly than beverages with a high EtOH concentration such as whiskey (Mellanby, 1919; Roine et al., 1993).

Alcoholic beverages are consumed in a variety of situations, including with meals and at social gatherings where food may or may not be consumed with the beverages. In bars and taverns, alcoholic beverages are often consumed in the absence of food or several hours after eating, at which time the stomach is empty or nearly so. These social settings more closely resemble the fasting condition than drinking with meals. The purpose of this study was to determine during the fasting state, the kinetics of alcohol absorption and elimination and peak BACs after drinking the same amount of EtOH in the form of beer (5.1% v/v), white table wine (12.5% v/v), and vodka (diluted to 20% v/v with tonic water).

MATERIALS AND METHODS

Subjects

Fifteen healthy, nonsmoking men between the ages of 25 to 65 were selected for participation after responding to an advertisement. Subjects were screened for underlying medical conditions through a standardized history and physical examination and routine chemistry and hematological tests. The Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire was used to evaluate subjects for possible alcohol-use disorders. Lifetime abstainers from alcohol and subjects with a score > 4 on the AUDIT-C, evidence of hypertension (blood pressure > 150/90), liver disease (including positive testing for hepatitis B or C), kidney disease, HIV infection, or other chronic illnesses based on history or biochemical parameters or hematological parameters were excluded from participation. Subjects with a body mass index (BMI) > 30 or < 18.5 were excluded. Subjects who were on any medications except occasional over-the-counter medications were excluded. Surreptitious smoking was evaluated by screening subjects with urine cotinine. Any subject with urine cotinine > 200 ng/ml was excluded.

Urine drug screens were performed at time of screening and on admission to the clinical research unit. A total of 66 men were screened to identify the 15 who participated in the study. The vast majority failed screening due to high AUDIT-C scores. Three participants were of European descent, 9 were African American, and 3 were Hispanic. The mean age of subjects was 37.8 years (range 26 to 55). The mean weight was 82.66 kg (range 68.6 to 96.4), and mean BMI was 26.35 (range 21.9 to 29.9).

Study Protocol

Subjects were required to abstain from alcoholic beverages for 48 hours prior to the study and to abstain from taking any over-the-counter or prescription medications including vitamins, with the exception of acetaminophen (< 1000 mg/d) for 14 days before the study. Subjects were admitted to the clinical research unit the day before the studies and remained as inpatients throughout the 3 days of study. The night before each study session, they were fed a standardized meal that was similar in composition on each of the days. Each subject was assigned a number, and all data were analyzed without personal identification. Subjects were monitored for adverse events throughout the entire period of the study from admission to discharge from the clinical research unit.

Administration of Alcoholic Beverages

Alcoholic beverages (0.5 g EtOH/kg body weight) were consumed over a 20-minute period beginning at 8 AM following an overnight fast. The volume of the alcoholic beverage was divided, so that half of the beverage was consumed within the first 10 minutes and the remainder within the next 10 minutes. Beer (5.1% v/v), white table wine (Chardonnay, 12.5% v/v), or vodka mixed with regular tonic to achieve a final concentration of 20% v/v was administered in a randomized fashion, so that 5 subjects received beer on day 1, 5 received wine on day 1, and 5 received vodka/tonic on day 1. The order of administration of the other beverages was also randomized on days 2 and 3. After a 20-minute period of consumption of the alcoholic beverages, the subjects remained fasting for 4 hours at which time they were allowed to eat a light lunch. All subjects completed each of the 3 beverage studies.

Blood Sampling

Venous blood samples were drawn from an indwelling catheter at specified times after administration of alcoholic beverages: Baseline, 10, 20, 30, 40, 60, 90, 120, 150, 180, 210, 240, 360, 480 minutes.

Analysis of Blood Ethanol

Whole BACs were analyzed at Mayo Laboratories (Rochester, MN) using head-space gas chromatography.

Pharmacokinetics Analysis

Noncompartmental analysis of individual concentration-time profiles was used to estimate the following pharmacokinetic (PK) measures:

- Peak concentration (C_{\max})
- Time to peak concentration (T_{\max})
- Area under the concentration–time curve (AUC): The AUC is a measure of exposure that integrates concentration across time. AUC was calculated using trapezoidal rule up to the last measured time point and was not extrapolated (using the typical linear extrapolation) due to the nonlinear PKs of alcohol.
- Mean residence time (MRT): The average time that drug remains in the body after administration (a time-based measure of exposure) was calculated as $AUMC/AUC$, where AUMC is the area under the moment curve, calculated from the concentration–time moment curve (concentration \times time vs. time) using the trapezoidal rule.
- Apparent clearance (CL_{app}) calculated as Dose/AUC.
- Volume of distribution (V_{ss}) = $MRT \times CL_{app}$
- Relative bioavailability: The relative bioavailability of alcohol following wine relative to spirits ($F_{W/S} = \frac{AUC_W \times Dose_S}{AUC_S \times Dose_W}$) and the

relative bioavailability of alcohol following beer relative to spirits ($F_{B/S} = \frac{AUC_B \times Dose_B}{AUC_S \times Dose_B}$) were estimated as measures of relative exposure following the beverages.

Statistical Analysis

Individual PK measures for each subject were tabulated and compared across sessions using repeated-measures analysis of variance (SPSS version 20.0; IBM, Armonk, NY). The level of statistical significance was set to 0.05. In case of significant differences, post hoc comparisons between sessions were performed using paired *t*-tests.

RESULTS

Figure 1 shows the geometric mean (\pm SD) BAC for all subjects versus time. As the profile indicates, the peak BAC was higher after consumption of vodka/tonic than wine or beer. The time required to reach the peak BAC was also earlier following vodka/tonic compared with wine or beer.

Analysis of PK parameters indicated statistically significant differences among beverage types for C_{max} , T_{max} , and AUC (Table 1). Statistical analysis using post hoc *t*-tests showed significant differences between all beverage pairs compared, such that the spirits (vodka/tonic) session showed the highest peak concentration and AUC, followed by wine and then by beer. The time to peak concentration was significantly shorter for spirits compared to wine and beer, while time to peak concentration did not differ significantly between wine and beer. MRT was shortest for spirits followed by wine and then by beer. These results indicate that spirits resulted in higher exposure compared to wine and beer, while beer resulted in lower and delayed exposure compared to spirits and wine.

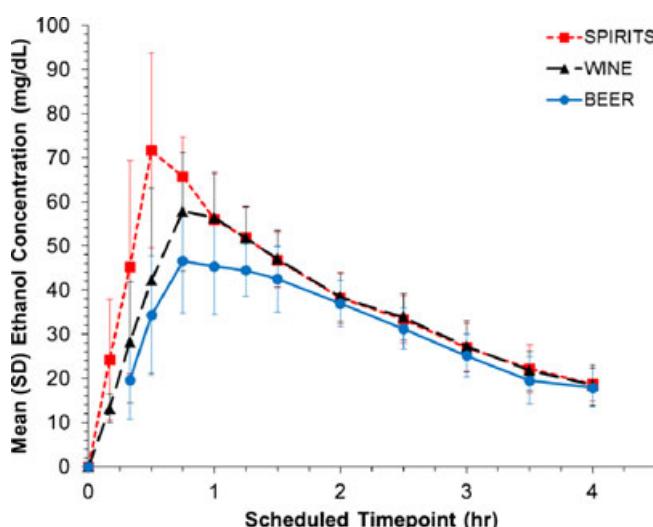


Fig. 1. Geometric mean values for blood alcohol concentrations following consumption of vodka/tonic (red squares), wine (black triangles), or beer (blue circles) are shown over time. Time zero represents initiation of consumption of beverages that was complete within 20 minutes.

The relative bioavailability for wine and beer relative to spirits was estimated from the AUC and adjusted for the absolute dose (in grams) administered. The estimated bioavailability for wine relative to spirits was 0.96 ± 0.13 (SE) and was not significantly different from the theoretical value of 1 for bioequivalent formulations. The estimated bioavailability of beer relative to spirits was 0.90 ± 0.02 (SE) and was significantly lower than the theoretical value of 1 for bioequivalent formulations. This finding implies that there is a 10% reduction in bioavailability of alcohol when administered as beer compared to spirits. Apparent clearance and volume of distribution showed higher values for beer compared to spirits or wine, probably resulting from the lower relative bioavailability of alcohol following wine and beer compared to spirits (Table 1).

In 14 of 15 subjects, the rate of absorption of spirits was greater than wine or beer. In 7 of the 15 subjects, the peak BAC exceeded 80 mg/dL (0.08%) after drinking vodka/tonic compared to beer or wine, and in 4 subjects, the peak BAC after vodka/tonic was more than 2-fold higher than after drinking beer. Peak BAC remained below 80 mg/dL in all subjects after consumption of this amount of beer or wine.

DISCUSSION

Our results show clearly that beer and wine are absorbed more slowly than vodka/tonic and that the peak BAC after drinking beer is significantly lower than the peak BAC after drinking a similar amount of EtOH as wine or vodka/tonic. The peak BAC after drinking wine was also significantly lower than after drinking vodka/tonic. In addition, the overall BAC exposure (AUC) following beer was lower than that for wine or vodka/tonic, which suggest a lower relative bioavailability for beer compared to the other beverages. While the estimated clearance for beer appears to be higher than that obtained for the other beverages, it is an “apparent” estimate because the route of administration is nonsystemic and artificially inflated as a result of the lower C_{max} and bioavailability for beer. Similarly, the apparent volume of distribution does appear to differ across beverages; however, this too may be confounded by the differences in bioavailability across the beverage types.

The beverages used in this study differ in both the concentration of EtOH and the caloric content of the beverages. The concentration of alcohol in beer was 5.1% v/v, wine was 12.5% v/v, and vodka was diluted to a concentration of 20% v/v in tonic. Thus, the concentration of EtOH in vodka/tonic (20%) was almost twice that of wine (12.5%) and 4 times the concentration of beer. Although this study was not designed to test the effect of concentration of alcoholic beverages directly, the findings suggest that, in the fasting state, less concentrated beverages such as beer and wine are absorbed more slowly than those that are more concentrated. Previous studies have not shown a consistent effect of concentration on the rate of absorption from different alcoholic beverages (Mellanby, 1919; Roine et al., 1993;

Table 1. Pharmacokinetic Parameters After Spirits, Wine, or Beer

PK Measure	Spirits	Wine	Beer	p-Value
C _{max} [mg%]	77.4 (17.0)	61.7 (10.8)	50.3 (9.8)	F(2,28) = 30.757, p < 0.001 t-tests: Spirits > Wine > Beer
T _{max} [hour]	0.6 (0.2)	0.9 (0.2)	1.0 (0.4)	F(2,28) = 12.103, p < 0.001 t-tests: Spirits > Wine = Beer
AUC [mg*h/l]	1,510.9 (216)	1,379 (219.9)	1,193.6 (184.1)	F(2,28) = 22.082, p < 0.001 t-tests: Spirits > Wine > Beer
MRT [hour]	1.7 (0.2)	1.8 (0.3)	1.8 (0.2)	F(2,28) = 3.968, p = 0.030 t-tests: Spirits = Wine > Beer
CL _{app}	27.7 (3.6)	29.4 (5.3)	31.0 (4.2)	F(2,28) = 6.527, p = 0.005 t-tests: Spirits = Wine < Beer
VD _{app}	46.3 (7.5)	51.7 (8.3)	56.6 (8.9)	F(2,28) = 14.291, p < 0.001 t-tests: Spirits < Wine < Beer

Results of post hoc *t*-tests are shown to compare results among the 3 conditions (spirits, wine, or beer). Values shown are the mean with standard error in parentheses.

PK, pharmacokinetics measure; C_{max}, peak blood alcohol concentration; T_{max}, time to peak concentration; AUC, area under the concentration-time curve; MRT, mean residence time; CL_{app}, apparent clearance; VD_{app}, volume of distribution.

Wilkinson et al., 1977). Both the caloric content and other minor constituents of beer, wine, or vodka/tonic could potentially influence the rate of absorption. Although the calories from EtOH in each beverage were constant, beer has more total calories than either wine or vodka/tonic due to the carbohydrate content. An 80 kg subject would have ingested 409 calories as beer, 334 calories as wine, and 297 calories as vodka/tonic. The caloric content of beer could play a role in our findings because gastric emptying is influenced by the calories ingested more than the composition of the meal (Calbet and MacLean, 1997; Velchik et al., 1989). However, the differences in peak BAC between wine and vodka/tonic which have similar caloric value suggest that concentration is a more important determinant of the rate of gastric emptying and/or absorption of EtOH. Our findings do not permit a way to evaluate the effects of minor components of the beverages.

The findings in this study confirm previous observations that alcoholic beverages are absorbed rapidly during the fasting state, reaching a peak BAC within 1 hour (Jones, 2000; Roine et al., 1993; Wilkinson et al., 1977). We observed that the peak BAC occurred much sooner after consumption of vodka tonic (0.60 ± 0.17 hours) than after drinking wine (0.91 ± 0.23 hours) or beer (1.04 ± 0.38 hours). This finding is internally consistent with differences in the rate of absorption of EtOH from beer, wine, or vodka/tonic.

EtOH is well absorbed by the intestinal mucosa (Gentry, 2000). As portal venous blood first passes through the liver before reaching the systemic circulation, the liver is exposed to most of the EtOH that is ingested. The liver is the primary site of metabolism of EtOH. Previous studies have shown that the bioavailability of EtOH is < 1 for very low doses of EtOH suggesting a possible "first-pass" effect (Gentry, 2000; Wilkinson et al., 1977). This effect is saturated at relatively low doses and thus would not apply to our findings. However, if alcoholic beverages are consumed and/or absorbed at a rate that is lower than the rate of metabolism and elimination by the liver, the amount of EtOH reaching target organs such as the brain would be negligible. The AUC reflects aggregate exposure of organs other than the liver to EtOH following ingestion

of alcoholic beverages. The AUC after consumption of beer was significantly lower (geometric mean 160.9) than after consumption of wine (177.5) or vodka/tonic (196.8). This finding suggests that the exposure of organs such as the brain to EtOH may be lower after drinking equivalent amounts of EtOH in the form of beer compared to wine or vodka/tonic in the fasting state. Although a different amount of EtOH (0.3 g/kg body weight) was ingested, Roine and colleagues (1993) reported similar findings in AUC for beer, wine, and undiluted whiskey (40%) when consumed in the fasting state.

These findings have implications for individuals who consume alcoholic beverages in the absence of food. Drinking more concentrated beverages such as vodka/tonic is highly likely to produce higher peak BAC than when the same amount of EtOH is consumed as beer or wine. Although 12 ounces of beer, 5 ounces of wine, and 1.5 ounces of liquor (80 proof) contain approximately the same amount of EtOH, the peak BAC and the aggregate exposure to EtOH of organs other than the liver and gut may differ significantly depending on the type of alcoholic beverage and the rate at which it is consumed. Rapid consumption of alcoholic beverages, particularly those that are highly concentrated, in the absence of food, should be discouraged.

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ALCOHOL METABOLISM

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The goal of this Review is to describe the pathways responsible for the metabolism of alcohol (ethanol) and understand the factors which regulate this oxidation. Understanding pathways of alcohol oxidation is important because it allows us to:

1. Learn how the body disposes of alcohol and its metabolites.
2. Discern some of the factors which influence this process.
3. Learn how alcohol influences the metabolism of nutrients and drugs.
4. May learn how alcohol damages various organs.
5. May help to identify individuals who are at increased or decreased risk for alcohol toxicity.

Some suggested causes for alcohol toxicity are linked to changes produced by the metabolism of ethanol such as redox state changes in the NAD⁺/NADH ratio, acetaldehyde formation, oxidative stress, and mitochondrial function are shown in **LIST 1** and will be discussed below. General reviews on alcohol metabolism can be found in (1–9).

Distribution of Alcohol in the Body

The equilibrium concentration of alcohol in a tissue depends on the relative water content of that tissue. Equilibration of alcohol within a tissue depends on the water content, rate of blood flow and the tissue mass. Ethanol is practically insoluble in fats and oils, although like water, it can pass through biological membranes. Ethanol distributes from the blood into all tissues and fluids in proportion to their relative content of water. The concentration of ethanol in a tissue is dependent on the relative water content of the tissue, and reaches equilibrium quickly with the concentration of ethanol in the plasma. There is no plasma protein binding of alcohol.

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The same dose of alcohol per unit of body weight can produce very different blood alcohol concentrations in different individuals because of the large variations in proportions of fat and water in their bodies, and the low lipid: water partition coefficient of ethanol. Women generally have a smaller volume of distribution for alcohol than men because of their higher percentage of body fat. Women will have higher peak blood alcohol levels than men when given the same dose of alcohol as g per kg body weight but no differences occur when given the same dose per liter of body water. First pass metabolism of alcohol by the stomach, which may be greater in males, may also contribute to the higher blood alcohol levels found in women (10,11).

The breath analyzer test for estimating blood alcohol concentrations is dependent on the diffusion of ethanol from pulmonary arterial blood into the alveolar air. The ethanol vapor in breath is in equilibrium with the ethanol dissolved in the water of the blood at a blood : breath partition coefficient of about 2100:1. An excellent recent review which summarizes many of these pharmacokinetic interactions can be found in (12).

Factors Affecting Alcohol Absorption

LIST 2 describes some factors which affect the absorption of alcohol. Absorption of alcohol from the duodenum and jejunum is more rapid than from the stomach, hence the rate of gastric emptying is an important determinant of the rate of absorption of orally administered alcohol.

1. Alcohol crosses biological membranes by passive diffusion, down its concentration gradient. Therefore, the higher the concentration of alcohol, the greater is the resulting concentration gradient, and the more rapid is the absorption.
2. Rapid removal of alcohol from the site of absorption by an efficient blood flow will help maintain the concentration gradient and thereby promote absorption.
3. Alcohol has irritant properties and high concentrations can cause superficial erosions, hemorrhages and paralysis of the stomach smooth muscle. This will decrease alcohol absorption,
4. Peak blood alcohol levels are higher if ethanol is ingested as a single dose rather than several smaller doses, probably because alcohol concentration gradient will be higher in the former case.
5. In general, there is little difference in the rate of absorption of the same dose of alcohol administered in the form of different alcoholic beverage i.e., blood ethanol concentration is not significantly influenced by the type of alcoholic beverage consumed.
6. The presence of food in the stomach retards gastric emptying and thus will reduce the absorption of alcohol, the “don’t drink on an empty stomach” concept. Meals high in either fat, or carbohydrate or protein are equally effective in retarding gastric emptying. The major factor governing the absorption rate of alcohol is whether the drink is taken on an empty stomach or together with or after a meal (13–15).

The blood alcohol concentration is determined by the amount of alcohol consumed, by the presence or absence of food in the stomach, factors which affect gastric emptying and the rate of alcohol oxidation.

First Pass Metabolism of Alcohol in the Stomach

Some of the alcohol which is ingested orally does not enter the systemic circulation but may be oxidized in the stomach by ADH isoforms such as σ ADH and class I and class III ADH. This first pass metabolism could modulate alcohol toxicity since its efficiency determines the bioavailability of alcohol. Ethanol is rapidly passed into the duodenum from the stomach in the fasted state. This will minimize first pass metabolism and thereby play a role in the higher blood alcohol concentrations observed in the fasted versus the fed state.

First pass metabolism has been reported to be low in alcoholics, especially in alcoholic women because of decreased ADH activity. This may be important in the increased sensitivity to alcohol and the higher blood alcohol concentrations in women than in men after an equivalent oral dose of ethanol. Several drugs, including H₂ receptor blockers such as cimetidine or ranitidine, or aspirin inhibit stomach ADH activity. This will decrease first pass metabolism by the stomach, and hence, increase blood alcohol concentrations.

The overall significance of first pass metabolism by the stomach is controversial. The speed of gastric emptying modulates gastric and hepatic first pass metabolism of alcohol. Considering the greater levels of alcohol metabolizing enzymes in the liver compared to the stomach, it seems likely that liver plays the major role in alcohol metabolism (16–18).

Alcohol Metabolism-General Principles (1–9)

LIST 3 describes some general principles of alcohol metabolism.

The major enzyme system(s) responsible for the oxidation of ethanol, alcohol dehydrogenase, and to a lesser extent, the cytochrome P450-dependent ethanol-oxidizing system, are present to the largest extent in the liver. Liver damage lowers the rate of alcohol oxidation and hence, elimination from the body. Ethanol is a nutrient and has caloric value (about 7 kcal per gram; carbohydrates and protein produce 4 kcal per gram, while fat produces 9 kcal). However, unlike carbohydrates (glycogen in liver and muscle) and fat (triglycerides in adipose tissues and liver) which can be stored and utilized in time of need e.g. fasting, alcohol is not stored and remains in body water until eliminated. Whereas metabolism of the major nutrients is under hormonal control, e.g insulin/glucagon, leptin, catecholamine, thyroid hormones, generally, there is little hormonal regulation to pace the rate of alcohol elimination. In view of these considerations, there is a major burden on the liver to oxidize alcohol in order to remove this agent from the body.

Animals with small body weight metabolize alcohol at faster rates than larger animals e.g. the rate of alcohol elimination in mice is 5 times greater than the rate in humans. These rates of alcohol metabolism correlate with the basal metabolic rate for that species, indicating that the capacity to oxidize ethanol parallels the capacity to oxidize the typical nutrients. However, it is important to note that alcohol-derived calories are produced at the expense of the metabolism of normal nutrients since alcohol will be oxidized preferentially over other nutrients (19–23).

Kinetics of Alcohol Elimination In-vivo (12–14)

Alcohol elimination was originally believed to be a zero-order process, meaning that alcohol was removed from the body at a constant rate, independent of the concentration of alcohol. Since the Km of most ADH isozymes for ethanol is low (about 1 mM), ADH is saturated at low concentrations of alcohol, hence, the overall elimination process proceeds at maximal velocity and is independent of the alcohol concentration. However, linearity is not observed at low alcohol concentration since ADH is no longer saturated with ethanol. Alcohol

elimination now follows Michaelis-Menten kinetics; the rate of change in the concentration of alcohol depends on the concentration of alcohol and the kinetic constants Km and Vmax (23,24).

In addition, because the metabolism of alcohol by CYP2E1 and some ADH isozymes, such as ADH4 involves a high Km for alcohol system, a concentration-dependent rate of ethanol elimination can be observed, with higher rates of alcohol elimination at higher blood alcohol concentrations. Because of this concentration dependence, it is not possible to estimate one single rate of alcohol metabolism. Concentration-dependent metabolism of alcohol has been observed in some, but not all studies on alcohol elimination (25,26).

Although rates vary widely, the “average” metabolic capacity to remove alcohol is about 170 to 240 g per day for a person with a body weight of 70 kg. This would be equivalent to an average metabolic rate of about 7 g/hr which translates to about one drink per hr. Since alcoholics may consume 200 to 300 g of ethanol per day, equivalent to 1400 to 2100 kcal, consumption of normal nutrients is usually significantly decreased (typically, 2000–3000 kcal consumed per day in the absence of alcohol).

Factors Modifying the Alcohol Elimination Rate

There is a 3–4 fold variability in the rate of alcohol elimination by humans because of various genetic and environmental factors described below.

Sex

There is a faster rate of alcohol elimination by women when rates are corrected for lean body mass. Since women have smaller body size and therefore smaller lean body mass, ethanol elimination per unit lean body mass is higher in women. Men and women generally have similar alcohol elimination rates when results are expressed as g per hr or g per liter liver volume. Because of first pass metabolism by the stomach, it is possible that a given oral dose of alcohol may produce a higher blood ethanol concentration in females than males (11,15).

Age

Very young animals have low alcohol elimination rates because ADH (and CYP2E1) are not fully expressed. Fetal liver eliminates alcohol very poorly which may have consequences for fetal alcohol syndrome. There may be a small decline in alcohol elimination with aging, perhaps due to decreased liver mass, or body water content.

Race

Alcohol elimination is reported to be somewhat higher in subjects expressing the beta3 class I ADH isoforms compared with individuals who only express the beta 1 isoform (see ADH alleles discussed below). Some studies, but not all, suggest an increased rate of alcohol elimination by native Americans compared to Caucasians. Rates of alcohol elimination by Chinese are similar to those of Caucasians. Liver mass may explain ethnic and gender differences in alcohol elimination rates. More research on possible population differences in alcohol elimination is required (27,28).

Food

Alcohol metabolism is higher in the fed nutritional state as compared to the fasted state because ADH levels are higher, and the ability of substrate shuttle mechanisms (see below) to transport reducing equivalents into the mitochondria is elevated. Food may also increase liver blood flow. The sugar fructose increases alcohol metabolism by providing substrates

which help to convert NADH to NAD⁺, and by enhancing mitochondrial oxygen uptake. The increase in the alcohol elimination rate by food was similar for meals of different compositions as there was no difference between carbohydrate, fat and protein on alcohol metabolic rate (29–31).

Biological Rhythms

The rate of alcohol elimination varies with the time of day, being maximal at the end of the daily dark period. This may be related to a body temperature cycle.

Exercise

In unclear literature, most studies report a small increase in alcohol elimination rate, perhaps due to increased body temperature or catecholamine release.

Alcoholism

Heavy drinking increases alcohol metabolic rate (see below). Advanced liver disease will decrease the rate of ethanol metabolism.

Drugs

Agents which inhibit ADH (pyrazoles, isobutyramide) or compete with ethanol for ADH (methanol, ethylene glycol) or which inhibit the mitochondrial respiratory chain will decrease the alcohol elimination rate. Antabuse (disulfiram) by inhibiting the elimination of acetaldehyde slows alcohol metabolism.

Scheme for Alcohol Metabolism—Fig 1 summarizes the basic overall metabolism of alcohol.

- Step 1** is catalyzed by the enzyme alcohol dehydrogenase, which is present largely in the liver, and consists of a family of isoforms. A vitamin-related cofactor, nicotinamide adenine dinucleotide (NAD) (derived from the vitamin niacin) is required to accept reducing equivalents (hydrogen atoms and electrons) from the alcohol. As a result, the ethanol is oxidized to the product acetaldehyde and the vitamin cofactor, NAD⁺ is reduced to the product NADH + H⁺ (note two hydrogens are removed from alcohol). The ADH reaction is reversible.
- Step 2** is catalyzed by the enzyme aldehyde dehydrogenase. Acetaldehyde is oxidized to acetate; NAD⁺ is the cofactor, and is reduced to NADH. The ALDH reaction is essentially irreversible. Much of the acetaldehyde produced from the oxidation of alcohol is oxidized in the liver to acetate; circulating levels of acetaldehyde are low under normal conditions.
- Step 3** Much of the acetate produced by the oxidation of acetaldehyde leaves the liver and circulates to peripheral tissues where it is activated to a key Acetyl CoA. Acetyl CoA is also the key metabolite produced from all major nutrients- carbohydrate, fat and excess protein. Thus, carbon atoms from alcohol wind up as the same products produced from the oxidation of carbohydrate, fat, and protein, including CO₂, fatty acids, ketone bodies, and cholesterol; which products are formed depends on the energy state and the nutritional and hormonal conditions.

ALCOHOL DEHYDROGENASE (4,32–34)

ADH is a zinc-containing enzyme, consisting of two subunits of 40 kDa each. It functions to oxidize endogenous alcohol produced by microorganisms in the gut, to oxidize exogenous ethanol and other alcohols consumed in the diet, and to oxidize substrates involved in steroid and bile acid metabolism. The enzyme has broad substrate specificity, oxidizing many primary or secondary alcohols. ADH is localized in the cytosolic fraction of the cell. ADH is found in highest amount in the liver, followed by GI tract, kidneys, nasal mucosa, testes, and uterus.

Multiple forms of ADH exist in human liver and their properties are reviewed in TABLE 1.

CLASS I ADH contains three genes, ADH1, ADH2 and ADH3 which code for the following subunits α (ADH1A), β_1 , β_2 and β_3 (ADH1B), and γ_1 and γ_2 (ADH1C). These different subunits and polymorphic forms can combine to produce a variety of homo- or hetero-dimers e.g., $\alpha\alpha$, $\beta_1\beta_1$, $\alpha\beta_2$. The forms are found primarily in the liver. The class I ADH forms are mainly responsible for the oxidation of alcohol. In a new classification, the family members have been classified into five distinct classes, designated ADH1 – ADH5, on the basis of the structural and kinetic characteristics. Human ADH genes that encode the subunit polypeptides α , β_1 , β_2 , β_3 , γ_1 , γ_2 , π , χ and (or named σ) are designated ADH1A (old ADH1), ADH1B*1 (old ADH2*1), ADH1B*2 (old ADH2*2), ADH1B*3 (old ADH2*3), ADH1C*1 (old ADH3*1), ADH1C*2 (old ADH3*2), ADH2 (old ADH4), ADH3 (old ADH5) and ADH4 (old ADH7), respectively. The ADH5 (old ADH6)-encoding polypeptide has not been given a Greek letter.

CLASS II ADH

The ADH4 gene codes for the π subunit, which produces $\pi\pi$ homodimers in the liver and to a lesser extent in kidney and lung. The high K_m for alcohol may make this enzyme more important in metabolism of high concentrations of alcohol.

CLASS III ADH

The ADH5 gene codes for the χ subunit which produces $\chi\chi$ homodimers. This isoform has a very high K_m for alcohol (>2 M).

CLASS V ADH

The mRNA product produced by the ADH6 gene is present in liver and stomach, but the protein has not been characterized.

CLASS IV ADH

The ADH7 gene encodes the sigma subunit which is very efficient in oxidizing retinol to retinal. This form is present in the stomach.

The class I ADH isoforms play the most important role in alcohol oxidation (33–37). ADH is present in low levels in fetal liver and the fetus eliminates ethanol very slowly because of this late maturation of ADH genes. The ability to form many isoforms, with varying kinetic properties, probably contributes to the large variability in the capacity for metabolizing alcohol that human populations exhibit. The strong sensitivity of the Class I ADH to pyrazole inhibition explains the powerful inhibition of alcohol metabolism by these agents.

Control of ADH activity is complex and involves:

- a) dissociation of the product NADH is rate limiting step
- b) subject to product inhibition by NADH and acetaldehyde

- c) subject to substrate inhibition by high concentrations of ethanol

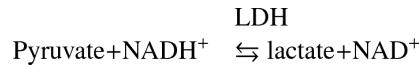
Alcohol oxidation is generally limited by the maximum capacity of ADH. The amount of ADH in the liver is greater in the fed than the fasted state which plays a major role in the increased rate of alcohol oxidation in the fed state (38,39). Inhibitors of ADH inhibit ethanol oxidation in direct proportion to their potency as inhibitors of ADH. Hormonal effects on ADH are complex; some stimulation is found after treatment with growth hormone, epinephrine or estrogens. Thyroid hormones and androgens inhibit ADH activity.

The polymorphic forms of ADH (Class I ADH1B, ADH1C) vary to some extent in different racial groups as shown in TABLE 2. To date, there are no clear associations between the various ADH isozymes and the development of alcoholic liver disease, or the susceptibility to alcohol actions, or the propensity to consume ethanol. Studies which have investigated the association between alcoholism and alcohol-induced liver damage with the ADH2, ADH3, CYP2E1 and ALDH2 polymorphisms are not conclusive. A large meta-analysis (36), showed that carriers of the *ADH2*1* and *ADH3*2* alleles, the less active ethanol metabolizing alcohol dehydrogenases, and the highly active *ALDH2*1* allele had an increased risk of alcoholism. This likely reflects low accumulation of acetaldehyde in these individuals. In liver disease, *ALDH2*1* is a protective factor as it removes toxic acetaldehyde. Neither the ADH2 nor the ADH3 polymorphism were implicated in the development of liver disease. Allelic variants of CYP2E1 were not involved in determining the risk of alcoholism or in alcoholic liver disease. Further research in this area is required, as is research on what other substrates the various ADH isoforms oxidize.

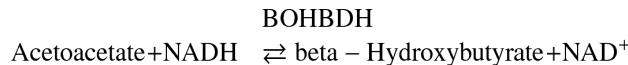
Hepatic Redox State (40–42)

Because the ADH and ALDH2 reactions reduce NAD⁺ to NADH, the cellular NAD⁺/NADH redox ratio is lowered as a consequence of ethanol metabolism. This has profound effects on other liver metabolic pathways which require NAD⁺ or are inhibited by NADH.

Since the ADH reactions occur in the cytosol, the cytosolic NAD⁺/NADH redox ratio will be lowered. This ratio is reflected by the pyruvate/lactate ratio because of the reaction.



Since the ALDH reaction occurs largely in the mitochondria, the mitochondrial NAD⁺/NADH redox ratio will be lowered. This reaction is reflected by the beta hydroxybutyrate/acetoacetate ratio because of the reaction.



Important reactions inhibited because of this decreased NAD⁺/NADH redox ratio are

1. Glycolysis
2. Citric Acid Cycle (ketogenesis favored)
3. Pyruvate Dehydrogenase
4. Fatty Acid Oxidation
5. Gluconeogenesis

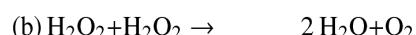
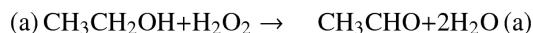
Reoxidation of NADH Generated by the ADH Reaction

To maintain effective rates of alcohol oxidation by ADH, it is important to regenerate NAD⁺ from the NADH produced by the ADH reaction. Under certain conditions, the rate of oxidation of alcohol can be limited by the reoxidation of NADH. The major system for reoxidizing NADH is the mitochondrial electron transfer system. By coupling NADH reoxidation to this system, energy will be produced from alcohol metabolism (7 kcal per g ethanol). Fig 2 shows the typical mitochondrial respiratory chain found in all tissues except the red blood cell. Note the 4 complexes which make up the chain. As electrons or reducing equivalents pass through complexes I, III and IV, an energized electrochemical and pH gradient is developed which is used to synthesize ATP via complex V, the ATP synthase (43,44).

Substrate Shuttles

Because intact mitochondria are not permeable to NADH, it is necessary to transfer the reducing equivalents of NADH present in the cytosol into the mitochondria by substrate shuttle mechanisms. The two major substrate shuttles are the α -glycerophosphate shuttle and the malate-aspartate shuttle (Fig 3). The malate-aspartate shuttle plays the major role in transferring reducing equivalents into the mitochondria (45–48). The rate of alcohol oxidation can be limited by the transfer of reducing equivalents into mitochondria or by the actual capacity of the respiratory chain to oxidize these reducing equivalents. Shuttle capacity may become limiting under fasting metabolic states as the levels of shuttle components decrease. This may contribute to the lower rates of alcohol oxidation (in addition to lower ADH content) in the fasting metabolic state. Agents or conditions which enhance reoxidation of NADH by the respiratory chain can increase the rate of alcohol metabolism e.g. uncoupling agents can accelerate ethanol oxidation in the fed metabolic state (38,39).

Catalase-Dependent Oxidation of Alcohol



Catalase, a heme containing enzyme, is found in the peroxisomal fraction of the cell. This is an important antioxidant enzyme since it normally catalyzes the removal of H₂O₂ (reaction b above) but it can also oxidize alcohol as shown in reaction (a) above. This pathway is limited by the rather low rates of H₂O₂ generation produced under physiological cellular conditions (less than 4 umol/g liver/hr, only 2% that of alcohol oxidation) and appears to have an insignificant role in alcohol oxidation by the liver.

A number of the central nervous system effects of ethanol are mediated by acetaldehyde. Because circulating acetaldehyde levels are very low, the metabolism of alcohol to acetaldehyde by the brain has been a major research area in alcohol research. Catalase is present throughout the brain, in the peroxisomes. Inhibitors of catalase were reported to depress oxidation of alcohol to acetaldehyde by the brain. Acetaldehyde derived from catalase-dependent oxidation of alcohol in the brain has been suggested to play a role in the development of tolerance to alcohol, to voluntary ethanol consumption and to the positive

reinforcing actions of ethanol, perhaps via interaction with catecholamines to produce various condensation products (49–51).

Microsomal (Cytochrome P450) Oxidation of Ethanol



Cytochrome P450s are a family of heme enzymes which are involved in the oxidation of steroids, fatty acids, and numerous xenobiotics ingested from the environment. Highest levels of cytochrome P450 are in the liver, where they are present mainly in the endoplasmic reticulum (microsomal fraction). Some P450's are also found in mitochondria. P450 functions in conjunction with other microsomal enzymes such as NADPH-cytochrome P450 reductase and cytochrome b5 (52–54). There are many isoforms of P450; over 100 gene families have been identified. The P450s arranged in families based on sequence homologies. CYP2E1 is a P450 which has the highest activity for oxidizing alcohol to acetaldehyde. Besides ethanol, CYP2E1 can oxidize many other compounds including acetone, benzene, and other alcohols. A clear physiological function for CYP2E1 has not been identified. Some of the significant properties of CYP2E1 are listed in **LIST 4** (55–58).

The Km of CYP2E1 for alcohol is 10 mM, 10-fold higher than the Km of ADH for ethanol but still within the range of alcohol concentrations seen in social drinking. At low alcohol concentrations, CYP2E1 may account for about 10% of the total alcohol oxidizing capacity of the liver. However in view of its higher Km, the relevance of CYP2E1 in ethanol oxidation increases as blood alcohol concentrations increase. Alcohol oxidation increases at higher ethanol concentrations, and much of this increase is due to CYP2E1 metabolism of alcohol. Many P450s are induced by their substrates; this helps to remove the xenobiotic from the body. CYP2E1 levels are increased by chronic ethanol administration by a mechanism largely involving protection of the enzyme against proteolysis by the macromolecular proteasome complex. CYP2E1 is also induced in diabetics, in the fasted nutritional state and by certain drugs. Because of its inducibility, CYP2E1 may play an important role in alcohol metabolism after chronic ethanol consumption, i.e. in alcoholics. As many as 13 different CYP2E1 polymorphisms have been identified. Some of these may be important as risk factors for carcinogenicity of tobacco or certain toxins; however, there is no evidence linking any of these polymorphisms to the frequency of alcohol liver damage.

Alcohol-Drug Interactions

Since ethanol and certain drugs compete for metabolism by CYP2E1, active drinkers will often display an enhanced sensitivity to certain drugs as alcohol will inhibit the metabolism of the drug and thereby prolong its half-life. Conversely, since CYP2E1 is induced after chronic alcohol consumption, metabolism of drugs which are also substrates for CYP2E1 will be increased. This will decrease the half-life of the drug, and thus decrease the effectiveness of the drug when ethanol is not present. CYP2E1 is very active in oxidizing many chemicals to reactive intermediates, e.g. carbon tetrachloride, benzene, nitrosamines, acetaminophen, halothane. Toxicity of these agents is enhanced in alcoholics (55,57–59).

The CYP2E1 catalytic turnover cycle results in the production of large amounts of reactive oxygen intermediates such as the superoxide radical and hydrogen peroxide. This may be important in mechanisms of alcoholic liver injury involving oxidative stress (60). Regulation of CYP2E1 is complex involving transcription, translational and protein turnover mechanisms.

Metabolic Adaptation (Tolerance)

Besides CNS adaptation, alcoholics (in the absence of liver disease) often display an increased rate of blood ethanol clearance. This is metabolic tolerance or adaptation. Suggested mechanisms for this metabolic tolerance are shown in **LIST 5** (55,61–63).

1. Class I ADH is not inducible. Further work with the many human isoforms is needed.
2. Substrate shuttle capacity and transport of reducing equivalents into the mitochondria is not altered by chronic alcohol consumption.
3. A major theory to explain metabolic adaptation – the “Hypermetabolic state hypothesis” – postulates that changes in thyroid hormone levels increases (Na⁺ + K⁺)-activated ATPase, with the subsequent increase of ADP levels. This increases the state 3 mitochondrial oxygen consumption, therefore, increasing NADH reoxidation. Increased oxygen consumption may cause hypoxia, especially to hepatocytes of zone 3 of the liver acinus, the region where alcohol toxicity originates (centrilobular hypoxia hypothesis).
4. CYP2E1 levels are enhanced after alcohol treatment Since CYP2E1 is the most active P450 for oxidizing alcohol, this may play an important role in metabolic tolerance.
5. Ethanol, perhaps via increasing endotoxin levels, may activate non-parenchymal cells such as Kupffer cells to release mediators (cytokines and prostaglandins) which stimulate oxygen consumption, thereby NADH reoxidation, by parenchymal cells.

The so-called swift increase in alcohol metabolism (SIAM) refers to an increased rate of ethanol metabolism within a few hours after alcohol administration *in vivo* or *in vitro*. Mechanisms responsible for SIAM are quite complex and appear to involve three major pathways, the mitochondria, the peroxisome and endotoxin activation of Kupffer cells (64).

Zonal Metabolism of Alcohol in the Hepatic Acinus (65–67)

Liver injury after chronic alcohol treatment originates in the perivenous zone of the hepatic lobule. Possible factors to explain this include:

1. Oxygenation is low in this zone since there is an oxygen gradient across the liver lobule and less oxygen reaches the hepatocytes in the perivenous zone. This is exacerbated after chronic alcohol administration which increases hepatic oxygen uptake, so even less oxygen reaches perivenous hepatocytes
2. & 3- ADH and ALDH2, and rates of alcohol and acetaldehyde metabolism are evenly distributed across the liver lobule. However, because of the lower oxygen tension, there is a more pronounced reduction of the hepatic redox state produced by ethanol in the perivenous zone
4. CYP2E1 is largely in the perivenous zone which explains why toxicity of drugs metabolized by CYP2E1 to reactive metabolites, e.g. CCl₄, or acetaminophen occurs in the perivenous zone.
5. Level of antioxidants, such as glutathione are lower in the perivenous zone.

Other Pathways of Alcohol Metabolism

1. Conjugation reactions

Ethanol can react with glucuronic acid to form ethylglucuronide. Such soluble conjugates are readily excreted. Cofactor availability and the poor affinity for alcohol by most conjugation enzymes limit these pathways. Ethyl glucuronide (68) is a non-volatile, water-soluble direct metabolite of ethanol. It can be detected in body fluids, tissue, sweat and hair for an extended time after alcohol has been eliminated from the body. These led to the suggestion that ethyl glucuronide may be a marker for alcohol consumption or for the detection of relapse of alcoholics. Ethyl glucuronide is not detectable in abstinent patients, non-drinkers or teetotalers and is thus specific for alcohol consumption.

3. Fatty Acyl Synthases

Fatty acid ethyl ester synthases catalyze the reaction between ethanol and a fatty acid to produce a fatty acyl ester. These synthases are present in most tissues, especially the liver and pancreas, organs most susceptible to alcohol toxicity (69). These esters are synthesized in the endoplasmic reticulum, and transported to the plasma membrane and then removed from the cell by binding to lipoproteins and albumin and transported in the circulation. Fatty acid ethyl esters can be toxic, inhibiting DNA and protein synthesis. When oxidative metabolism of ethanol is blocked, there is an increase in ethanol metabolism to the fatty acid ethyl ester. These esters can be detected in the blood after alcohol is no longer detectable and therefore detection of fatty acid ethyl esters may serve as a marker of alcohol intake.

Acetaldehyde Metabolism

The balance between the various ADH and ALDH isoforms regulates the concentration of acetaldehyde, which is important as a key risk factor for the development of alcoholism (70–74). Most of the acetaldehyde produced from the oxidation of alcohol is further oxidized in the liver by a family of ALDH isoforms. Major ALDH isoforms exist in the mitochondrial, microsomal, and cytosolic compartments. Mitochondria contain a low Km ALDH in the matrix space (class II ALDH) and a high Km ALDH in the outer membrane, microsomes contain a high Km ALDH, while the cytosol contains an intermediate (class I ALDH) and a high Km (class III ALDH) ALDH. Acetaldehyde can also be oxidized by aldehyde oxidase, xanthine oxidase, and by CYP2E1, but these are insignificant pathways. The low Km mitochondrial ALDH oxidizes most of the acetaldehyde produced from the oxidation of alcohol, although in human liver, the class I cytosolic ALDH may also contribute (75). The class I and II ALDHs are tetrameric enzymes, with subunit molecular weights of 54 kDa.

In general, the capacity of ALDH to remove acetaldehyde exceeds the capacity of acetaldehyde generation by the various pathways of alcohol oxidation. Therefore, circulating levels of acetaldehyde are usually very low. Chronic alcohol consumption decreases acetaldehyde oxidation, either due to decreased ALDH2 activity or to impaired mitochondrial function. Acetaldehyde generation is increased by chronic alcohol consumption because of metabolic adaptation. As a result, circulating levels of acetaldehyde are usually elevated in alcoholics because of increased production, decreased removal or both.

The basis of action for certain alcohol-aversive drugs such as disulfiram (Antabuse) or cyanamide is to inhibit ALDH, and therefore alcohol oxidation. The resulting accumulation of acetaldehyde causes a variety of unpleasant effects such as nausea, sweating, vomiting, and increased heart rate, if ethanol is consumed with these drugs. Certain individuals, usually of Asian extraction, have an inactive mitochondrial ALDH2 because of a single amino acid substitution; glutamate 487 is converted to a lysine residue; this causes a large

decrease in affinity for the NAD⁺ cofactor. Thus inactive enzyme can be found in 15 to 40% of the population of East Asia and when these individuals consume ethanol, blood levels of acetaldehyde are 5-to 20-fold higher than those found in individuals with the active ALDH allele. Individuals with the inactive ALDH show marked vasodilator, nausea and dysphasia when consuming alcohol, and are virtual abstainers if homozygous for the *ALDH2**2 allele. Acetaldehyde is poorly eliminated by these individuals and as a consequence, little alcohol is consumed. ALDH2 deficient individuals are at lower risk for alcoholism. They may have possible increased risk for liver damage if alcohol continues to be consumed.

Acetaldehyde is a reactive compound and can interact with thiol and amino groups of amino acids in proteins. Formation of acetaldehyde adducts with proteins may cause inhibition of that protein's function and/or cause an immune response (73,74). ALDH is important not only for removing acetaldehyde, but also for the removal of other aldehydes, including biogenic aldehydes and lipid peroxidation-derived aldehydes. Effective removal of acetaldehyde is important not only to prevent cellular toxicity, but also to maintain efficient removal of alcohol, e.g., acetaldehyde is a product inhibitor of ADH. The class I ALDH can oxidize retinal to retinoic acid; the possibility that high levels of acetaldehyde compete with retinal for oxidation by class I ALDH may be of developmental significance (75).

Future Considerations

While much has been learned about the pathways of ethanol metabolism and how these pathways are regulated, there are many critical questions remaining. For example:

- What limits and regulates alcohol metabolism in-vivo?
- What is the mechanism(s) responsible for metabolic tolerance?
- Is it alcohol per se, or alcohol-derived metabolites which play a key role in organ damage? What might be the consequences of attempting to accelerate ethanol metabolism?
- What is the role, if any, of the various ADH isoforms in oxidation of endogenous substrates, alcohol metabolism and alcohol toxicity? The hypothesis that alcohol or acetaldehyde inhibit the oxidation of physiologically important endogenous substrates of ADH or ALDH2 and that this may contribute to the adverse action of ethanol requires further study.
- Can the various ADH and ALDH isozymes or polymorphic forms of CYP2E1 be of predictive value or serve as markers to identify individuals who are susceptible to developing alcoholism? Can non-invasive probes be developed to measure the various isoforms present?
- Are there population and gender differences in rates of alcohol elimination, and if so, are such differences explained by the varying isoforms present in that population?
- What controls the expression of the various isoforms at the transcriptional level, and are there posttranscriptional modifications? What dictates the turnover of these enzymes which may be important in regulating the amount of active enzyme present in the cells, e.g. CYP2E1?
- Why are calories from alcohol not as efficient in providing energy as are calories from typical nutrients? What is the mechanism by which food increases alcohol metabolism?
- What role, if any, does acetate play in the metabolic actions of alcohol?

- Can we build appropriate models and rate equations to kinetically describe the process of alcohol elimination under various conditions? [author query: the Guest Editor has requested this section be replaced with a “conclusions” paragraph.]

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KEY POINTS

The equilibrium concentration of alcohol in a tissue depends on the relative water content of that tissue.

The rate of alcohol absorption depends on the rate of gastric emptying, the concentration of alcohol and is more rapid in the fasted state.

The blood alcohol concentration is determined by the amount of alcohol consumed, the presence or absence of food and the rate of alcohol metabolism.

First pass metabolism of alcohol occurs in the stomach and is decreased in alcoholics.

Liver alcohol dehydrogenase is the major enzyme system for metabolizing alcohol; this requires the cofactor NAD and the products produced are acetaldehyde and NADH.

The acetaldehyde is further oxidized to acetate, the same final metabolite produced from all other nutrients-carbohydrates, fats and proteins; the acetate can be converted to CO₂, fatty acids, ketone bodies, cholesterol and steroids.

Oxidation of alcohol by cytochrome P450 pathways, especially CYP2E1 which is induced by alcohol, are secondary pathways to remove alcohol especially at high concentrations.

Alcohol metabolism is regulated by the nutritional state, the concentration of alcohol, specific isoforms of alcohol dehydrogenase, need to remove acetaldehyde and regenerate NAD and induction of CYP2E1.

Substrate shuttles and the mitochondrial respiratory chain are required to regenerate NAD from NADH, and this can limit the overall rate of alcohol metabolism.

Metabolism of alcohol is increased in alcoholics without liver disease: this metabolic tolerance to alcohol may involve induction of CYP2E1, elevated regeneration of NAD or endotoxemia.

SYNOPSIS

This review describes the pathways and factors which modulate blood alcohol (alcohol and ethanol are used interchangeably) levels and alcohol metabolism and describe how the body disposes of alcohol. The various factors which play a role in the distribution of alcohol in the body, influence the absorption of alcohol and contribute to first pass metabolism of alcohol will be described. Most alcohol is oxidized in the liver and general principles and overall mechanisms for alcohol oxidation will be summarized. The kinetics of alcohol elimination in-vivo and the various genetic and environmental factors which can modify the rate of alcohol metabolism will be discussed. The enzymatic pathways responsible for ethanol metabolism, in particular, the human alcohol dehydrogenase alleles will be described. Rate-limiting steps in the overall metabolism of ethanol, including the activity of alcohol dehydrogenase isoforms, and the necessity to reoxidize NADH by substrate shuttle pathways and the mitochondrial respiratory chain will be discussed. The impact of alcohol metabolism on other liver metabolic pathways, and on cytochrome P450-dependent metabolism of xenobiotics and drugs will be briefly described. Factors playing a role in the metabolic adaptation i.e., increased rate of ethanol metabolism by chronic alcoholics will be discussed. The metabolism and role of acetaldehyde in the toxic actions of alcohol and ethanol drinking behavior will be discussed. Despite much knowledge of alcohol pharmacokinetics and metabolism, numerous questions remain for further evaluation and research, including what regulates alcohol metabolism in-vivo, the role of alcohol metabolites in organ damage, functions and physiological substrates of the various ADH isoforms, population and gender differences in alcohol metabolism, need for developing markers to identify individuals susceptible to alcohol and other considerations are discussed.

LIST 1**SOME SUGGESTED CAUSES FOR ALCOHOL TOXICITY**

- Redox state changes in the NAD/NADH ratio
- Acetaldehyde formation
- Mitochondrial damage
- Cytokine formation (TNF α)
- Kupffer cell activation
- Membrane actions of ethanol
- Hypoxia
- Immune actions
- Oxidative stress

LIST 2**Factors Affecting Alcohol Absorption**

1. Concentration of alcohol
2. Blood flow at site of absorption
3. Irritant properties of alcohol
4. Rate of ingestion
5. Type of beverage
6. Food

LIST 3**GENERAL PRINCIPLES OF ALCOHOL OXIDATION**

1. < 10 % alcohol excreted in breath, sweat and urine.
2. ~ 90 % alcohol removed by oxidation.
3. Most of this alcohol oxidation occurs in the liver.
4. Alcohol cannot be stored in the liver.
5. No major feedback mechanisms to pace the rate of alcohol metabolism to the physiological conditions of the liver cell.

LIST 4**CYTOCHROME P4502E1 (CYP2E1)**

A minor pathway for alcohol metabolism

Produces acetaldehyde, 1-hydroxyethyl radical

Responsible for alcohol-drug interactions

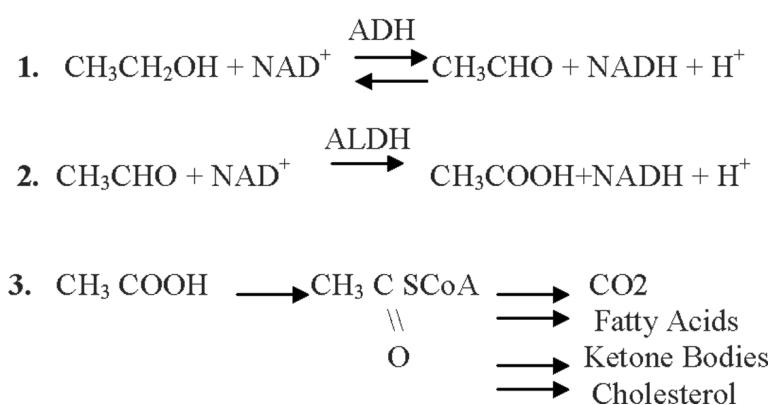
Activates toxins such as acetaminophen, CCl₄, halothane, benzene, halogenated hydrocarbons to reactive toxic intermediates

Activates procarcinogens such as nitrosamines, azo compounds to active carcinogens

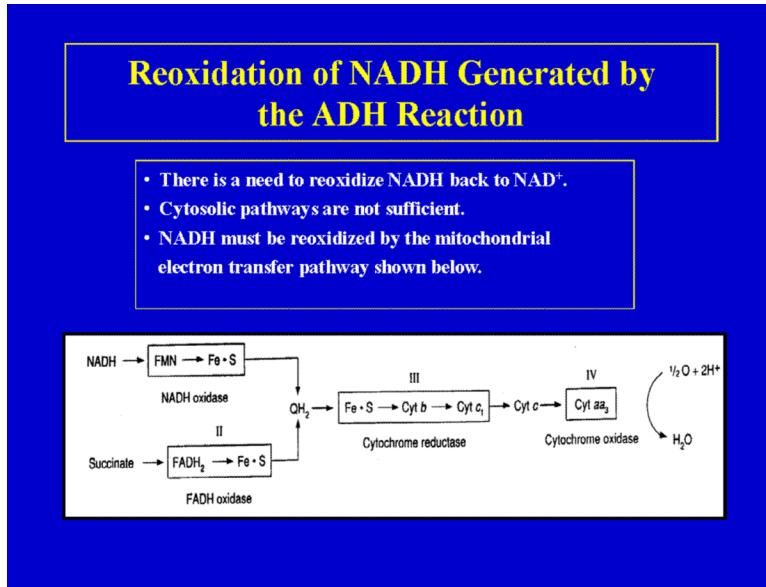
Activates molecular oxygen to reactive oxygen species such as superoxide radical anion, H₂O₂, hydroxyl radical

LIST 5**SUGGESTED MECHANISMS FOR METABOLIC TOLERANCE TO ALCOHOL**

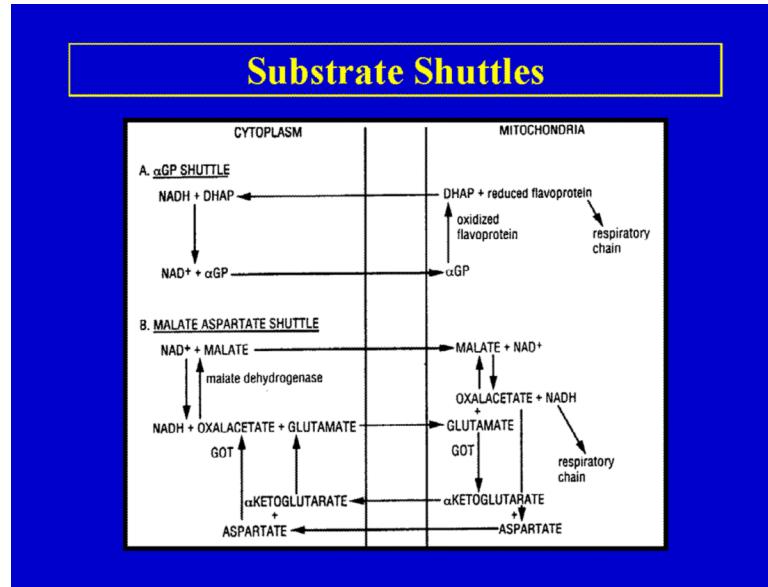
- Induction of alcohol dehydrogenases
- Increased shuttle capacity
- Increased reoxidation of NADH by mitochondria
- Induction of CYP2E1
- Hypermetabolic state
- Increased release of cytokines or prostaglandins which elevate oxygen consumption by hepatocytes

GENERAL SCHEME FOR ETHANOL OXIDATION**Fig 1.**

General scheme for alcohol oxidation. Alcohol is oxidized by alcohol and aldehyde dehydrogenases eventually to acetyl CoA. Depending on the nutritional, hormonal, energetic status, the acetyl CoA is converted to the indicated products.

**Fig 2.**

The mitochondrial respiratory chain. Reducing equivalents (electrons) enter the respiratory chain either from NADH or from succinate and are passed through a series of electron carriers to cytochrome oxidase which reacts with molecular oxygen to produce water. The NADH produced from the oxidation of alcohol by alcohol dehydrogenase is oxidized by the respiratory chain. Energy, in the form of ATP, is produced during this oxidation, hence, alcohol is of caloric value.

**Fig 3.**

Substrate shuttle mechanisms for the reoxidation of NADH by the mitochondrial respiratory chain. The alcohol dehydrogenase reaction oxidizes alcohol in the liver cytosol and therefore produces NADH in the cytosol. This NADH cannot directly enter the mitochondria for oxidation (Fig 2) and therefore has to be transported into the mitochondria by either the α -glycerophosphate (a) or the malate-aspartate (b) shuttle.

TABLE 1

Kinetic constants for human liver ADH isoforms

Constant	α	$\beta_1\beta_1$	$\beta_2\beta_2$	$\beta_3\beta_3$	$\gamma_1\gamma_1$	$\gamma_2\gamma_2$	π
K_m NAD ⁺ , μM	13	7.4	180	550	7.9	8.7	14
K_m ethanol, mM	4.2	0.049	0.94	24	1	0.63	34
K_i 4-methylpyrazole, μM	1.1	0.13	-	2.1	0.1	-	2000
V_{max} min ⁻¹	27	9.2	400	300	87	35	20
pH-optimum	10.5	10.5	8.5	7.0	10.5	10	10.5

TABLE 2

Frequency of ADH Alleles in Racial Populations

	ADH1B*1	ADH1B*2	ADH1B*3	ADH1C*1	ADH1C*2
White-American	>95%	<5%	<5%	50%	50%
White-European	85%	15%	<5%	60%	40%
Japanese	15%	85%	<5%	95%	5%
Black-American	85%	<5%	15%	85%	15%