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ORIGINAL ARTICLE

Ultra-rapid rate of ethanol elimination from blood in drunken drivers with extremely high blood-alcohol concentrations

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Abstract The rate of alcohol elimination from blood was determined in drunken drivers by taking two blood samples about 1 h apart. These cases were selected because the individuals concerned had reached an extremely high blood-alcohol concentration (BAC) when they were apprehended. This suggests a period of continuous heavy drinking leading to the development of metabolic tolerance. Use of double blood samples to calculate the elimination rate of alcohol from blood is valid provided that drunken drivers are in the post-absorptive phase of the BAC curve, the time between sampling is not too short, and that zero-order elimination kinetics operates. Evidence in support of this came from other drunken drivers in which three consecutive blood samples were obtained at hourly intervals. The mean BAC (N=21) was 4.05 g/l (range, 2.71–5.18 g/l), and the average rate of alcohol elimination from blood was 0.33 g l^{-1} h^{-1} with a range of 0.20–0.62 g l^{-1} h^{-1}. The possibility of ultra-rapid rates of ethanol elimination from blood in drunken drivers having extremely high BAC deserves to be considered in forensic casework, e.g., when retrograde extrapolations and other blood-alcohol calculations are made. The mechanism accounting for more rapid metabolism is probably related to induction of the microsomal enzyme (CYP2E1) pathway for ethanol oxidation, as one consequence of continuous heavy drinking. However, the dose of alcohol and the duration of drinking necessary to boost the activity of CYP2E1 enzymes in humans have not been established.

Keywords Alcohol · Blood · Elimination rate · Metabolism · Drunk driving

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Introduction

Ethanol is an example of a drug displaying dose-dependent or saturation kinetics, and the elimination stage of the blood-alcohol concentration (BAC) curve is best described by Michaelis–Menten kinetics [9, 14, 47, 50]. Human metabolism of ethanol occurs primarily in the liver in a reaction catalyzed by class I isozymes of alcohol dehydrogenase (ADH), which have a low k_m corresponding to a BAC of 0.05–0.1 g/l [43, 57]. Accordingly, the oxidative metabolism of ethanol occurs at a maximum velocity provided that BAC exceeds 0.2 g/l so that the ADH enzyme remains saturated with substrate [6, 7]. Studies have shown that the slope of the declining part of the BAC curve, which is a reflection of the elimination rate of alcohol from blood, averages about 0.15 g l^{-1} h^{-1} in moderate drinkers, with a range of 0.1–0.25 g l^{-1} h^{-1} for most people [18, 60, 61].

Besides the involvement of cytosolic ADH in the metabolism of ethanol, there are oxidative enzymes also located in the microsomal fraction of the hepatocytes denoted CYP2E1 [38, 39]. The CYP2E1 enzyme has a higher k_m for oxidation of ethanol (0.5–0.6 g/l) and, therefore, plays a more important role in metabolism of ethanol after heavy drinking, as what occurs in many drunk drivers [33, 40]. Moreover, studies have shown that the activity of CYP2E1 increases appreciably after a period of continuous heavy drinking as a consequence of enzyme

induction (increased synthesis), which leads to a faster oxidation of substrates [5, 21, 30]. However, the dose of alcohol and the duration of drinking necessary to boost the activity of CYP2E1 in humans have never been determined empirically [2, 48].

This paper concerns elimination rates of ethanol from blood in drunk drivers calculated from the change in BAC between two points in time. The main focus of this article concerns drunk drivers who had consumed enormous quantities of alcohol to reach extremely high BAC when they were apprehended. This verifies continuous heavy drinking and the development of pronounced metabolic tolerance.

Materials and methods

Blood samples and determination of ethanol

Sweden operates a two-tier per se BAC legal limit for driving with threshold values set at 0.20 mg/g (~0.2 g/l) and 1.0 mg/g (~1.0 g/l). The corresponding statutory breath-alcohol limits in Sweden are 0.10 and 0.50 mg/l [24]. BACs are reported in this article in mass/volume units (g/l) to comply with international standards. If the concentration had instead been expressed as weight/weight units e.g. 1.0 mg/g or 1.0 g/kg becomes 1.06 g/l when converted to weight/volume, assuming a density of whole blood of 1.06 g/ml [34].

After obtaining a positive roadside breath-alcohol screening test, drunken drivers are required to submit to an evidential breath-alcohol test. Refusal to comply with the breath-testing procedure means that a specimen of venous blood will be taken and, if necessary, by force. Two tubes of blood (8–10 ml) are taken with the aid of evacuated tubes (10 ml), each containing sodium fluoride (100 mg) and potassium oxalate (25 mg) as preservatives (Terumo Europe NV, Leuven, Belgium). After cleaning the skin with soap and water, two sterile evacuated tubes are filled with blood in rapid succession after a cubital vein is punctured.

The concentration of ethanol in blood from drunken drivers is determined by headspace gas chromatography (HS-GC) as described in more detail elsewhere [20]. All determinations were made in triplicate, and the aliquots (100 μl) of blood were removed from both tubes and diluted with 1 ml of aqueous *n*-propanol (0.08 g/l), which serves as the internal standard for gas chromatographic analysis. The calibration plot for this analytical method is linear over a wide concentration range (0–5.0 g/l) that might be encountered in routine forensic casework.

According to current laboratory practice, a BAC<0.10 g/l is reported as negative [17]. Furthermore, a deduction is always made from the mean concentration to compensate for random and systematic errors in the analytical procedures. However, for the purpose of this study, the average BAC (mean of triplicates), without making a deduction for uncertainty, was used to calculate the elimination rate of alcohol.

Measuring the elimination rate of ethanol from blood

The elimination rate of alcohol from blood was determined from the change in BAC between double blood samples taken about 1 h apart using the following simple equation:

$$\left[(\mathrm{BAC}_1 - \mathrm{BAC}_2) \Big/ \mathrm{min}_{\mathrm{diff}}\right] \mathrm{x}\ 60$$

where BAC_2 and BAC_1 are the mean concentrations of alcohol determined in the second and the first blood sample, respectively [46, 51]. The change in BAC was then divided by the time difference in minutes (min_{diff}) and multiplied by 60 to obtain the elimination rate per hour. In some drunk-driving suspects, three samples of blood were taken at roughly hourly intervals that permitted making three different estimates of the elimination rate of alcohol in each individual.

Results

Blood-alcohol elimination rate in drunken drivers

Figure 1 shows a relative frequency distribution of the elimination rates of alcohol from blood in over 1,000 drunk drivers as derived from double blood samples [25]. This distribution was a good fit to a Gaussian bell-shaped curve having a mean (median) value of 0.19 g l^{-1} h^{-1} (0.187 g l^{-1} h^{-1}) and 2.5 and 97.5 percentiles of 0.11 and 0.31 g l^{-1} h^{-1}, respectively. There were 24 cases (2.2%) with apparent ethanol elimination rates below 0.1 g l^{-1} h^{-1}, and these individuals had probably not entered the post-absorptive phase of the BAC curve when the first blood specimen was taken.

Alcohol elimination rate derived from three successive blood samples

Support for the practice of using double blood samples to calculate the elimination rate of alcohol from blood was obtained from the data presented in Table 1. Five drunk drivers submitted three sets of blood samples for determination of alcohol, and this meant that the elimination rate of alcohol could be calculated in three different ways. Regardless of which pair of blood samples was used in the

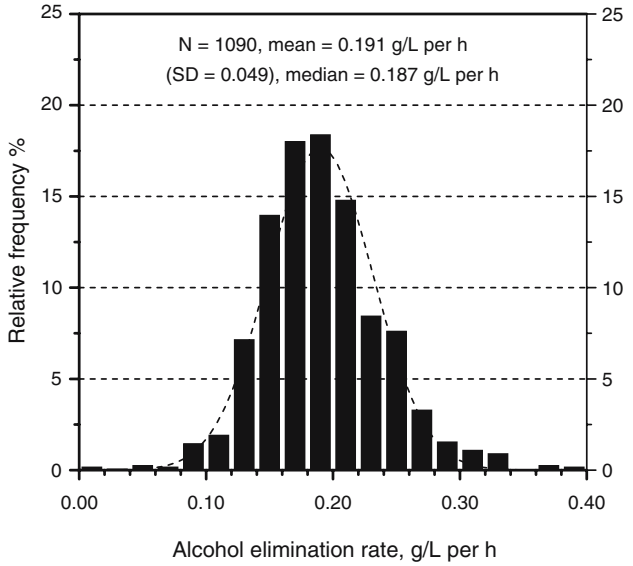

Fig. 1 Frequency distribution of elimination rate of ethanol from blood in drunken drivers derived from double blood samples taken ~1 h apart

calculation, the elimination rate of alcohol showed good agreement within each subject.

Analysis of variance (ANOVA) showed a significant variation between subjects in their ability to eliminate alcohol from blood compared with variation within subjects (F=18.2 and degrees of freedom=4 and 10; p<0.001). The mean elimination rate of alcohol from blood was 0.19 g l^{-1} h^{-1} (range 0.14–0.24), and the mean BAC was 2.15 g/l (range, 1.67–2.48 g/l).

Ultra-rapid rate of alcohol elimination in drunk drivers

Table 2 presents information about drunk drivers with unusually high BAC when they were apprehended by the police. The mean BAC was 4.05 g/l (range 2.71–5.18), and there were 5 women (23%) and 16 men (76%) among the suspects with a mean age of 41 and 49 years, respectively. The starting BAC was about the same regardless of gender, being 4.07 g/l for the women and 4.04 g/l for the men.

The rate of ethanol elimination from blood averaged 0.33 g l^{-1} h^{-1} and ranged from 0.20–0.62 g/l for the 21 individuals depicted in Table 2. Women had a slightly higher capacity to eliminate alcohol from blood than men, averaging 0.37 g l^{-1} h^{-1} compared with 0.32 g l^{-1} h^{-1} for men. These ultra rapid elimination rates of ethanol can be compared with a mean value of 0.19 g l^{-1} h^{-1} in over 1,000 drunk drivers (Fig. 1) and 0.15 g l^{-1} h^{-1} in moderate drinkers after a bolus dose of ethanol [18, 61].

Table 1 Inter-subject and intra-subject variation in the rate of alcohol elimination from blood (g l^{-1} h^{-1}) in drunken drivers providing three consecutive blood samples

Case	Time of blood sample	Concentration (g/l)[a]	Blood pair	Alcohol elimination rate (g l^{-1} h^{-1})
1a	20:39	2.48	1a_1b	0.19
1b	21:42	2.28	1a_1c	0.20
1c	22:05	2.20	1b_1c	0.21
2a	20:23	2.21	2a_2b	0.24
2b	21:23	1.97	2a_2c	0.21
2c	22:20	1.67	2b_2c	0.20
3a	21:20	2.31	3a_3b	0.15
3b	22:21	2.16	3a_3c	0.14
3c	23:05	2.06	3b_3c	0.14
4a	20:39	2.47	4a_4b	0.19
4b	21:42	2.27	4a_4c	0.20
4c	22:05	2.19	4b_4c	0.21
5a	05:55	2.17	5a_5b	0.21
5b	06:15	2.10	5a_5c	0.20
5c	07:35	1.83	5b_5c	0.20

[a] Mean of duplicate or triplicate determination

Table 2 Elimination rates of alcohol from blood in drunken drivers with very high blood-alcohol concentration (BAC) when apprehended

Subject	Age and gender	Time of day[a]	BAC-1[b] g/l	BAC-2[c] g/l	Time difference (min)	Alcohol elimination rate (g l^{-1} h^{-1})
1	30 f	16:30	5.18	4.61	85	0.40
2	58 m	16:38	4.37	4.11	62	0.25
3	43 m	00:05	4.33	3.92	60	0.41
4	42 m	19:30	3.91	3.52	60	0.39
5	60 m	12:00	4.21	4.03	55	0.20
6	48 m	13:35	4.15	3.77	65	0.35
7	33 f	01:30	2.98	2.77	25	0.50
8	53 m	17:50	3.96	3.70	55	0.28
9	59 m	19:00	4.13	3.95	35	0.31
10	41 m	19:50	4.63	4.19	66	0.40
11	60 f	19:10	4.12	3.79	61	0.32
12	33 m	23:15	2.71	2.33	67	0.34
13	53 f	00:30	3.87	3.49	65	0.35
14	54 m	18:30	3.76	3.49	65	0.25
15	52 m	13:40	3.83	3.70	35	0.22
16	50 m	18:13	4.03	3.80	60	0.23
17	42 m	09:00	4.53	3.81	70	0.62
18	57 m	11:05	4.03	3.67	55	0.39
19	51 m	12:50	4.12	3.84	60	0.28
20	52 m	12:35	4.09	3.89	50	0.24
21	31 f	23:00	4.23	3.96	63	0.26

[a] Time of first blood sample
[b] Mean BAC for the first sample
[c] Mean BAC for the second sample

Discussion

The disposition and fate of alcohol in the body has probably been studied more extensively than any other medicinal or recreational drug. This depends, at least in part, on the early availability of a reliable analytical method, the so-called Widmark micro-method, which was published in the 1920s [59]. The principal features of absorption, distribution, and elimination of ethanol, the relative amounts excreted unchanged in breath and urine, the effects of food on the shape of the blood-alcohol curve, and rates of elimination from the bloodstream were documented many years ago [15, 27, 60].

Little is known about the elimination rate of ethanol from blood in drunken drivers based on actual experiments for the simple reason that controlled studies are not possible with these individuals. However, because zero-order kinetics operates for much of the time that ethanol is metabolized, taking two blood samples about 1 h apart furnishes another way to calculate the elimination rate of alcohol [13, 42, 46]. Support for the double blood sample method comes from the results presented in Table 1, showing instances when drunken drivers gave three successive blood samples. Regardless of which pair of bloods were used in calculating, the elimination rate of alcohol the results agreed well within the same individual. For best results, the two samples of blood should not be taken too close together, and a 60-min interval seems appropriate.

When double blood samples were obtained from over 1,000 drunk drivers, the mean elimination rate of alcohol from blood was 0.19 g l^{-1} h^{-1}, and the 2.5 and 97.5 percentiles were 0.11 and 0.31 g l^{-1} h^{-1}, respectively [25]. Some individuals exhibited an ultra-rapid elimination rate exceeding 0.35 g l^{-1} h^{-1}, whereas others had unusually slow elimination rates, which might be interpreted to mean that absorption of alcohol was incomplete at the time the first blood sample was taken. Drinking after a meal is known to delay gastric emptying, and instead of a sharp peak followed by a swift decline, the maximum of the BAC curve is more like a plateau [23, 27, 29, 36, 58].

Strong support exists that most drunken drivers have entered the elimination phase of the BAC curve when the first blood-sample is obtained at about 60 min after arrest [21, 35, 42]. An even longer time must have elapsed after the end of drinking. Although the time required for reaching C_{max} (usually denoted as t_{max}) is never known in the individual case, many studies show that absorption is essentially complete by 60 min with a range of 5–120 min [18, 62]. Accordingly, the method of double blood samples is one way to investigate the rate of alcohol elimination from blood for the vast majority of drunken drivers.

Limitations of the method of double blood sampling should also be mentioned. First and foremost, the time of sampling blood recorded by the police or physician must be accurate and trustworthy. The abnormally high rate of 0.62 g l^{-1} h^{-1} (Table 2) can be considered suspect, and timing of one or both blood samples might have been incorrect. Abnormally low elimination rates of alcohol are likely if the person has not entered the post-absorptive phase when the first blood sample was drawn. In Fig. 1, there were 24 cases (2.2%) having elimination rates of alcohol of less than 0.1 g l^{-1} h^{-1}, and these probably are individuals with slow absorption of alcohol. With a rapid gastric emptying, C_{max} occurs earlier after end of drinking and is generally followed by a diffusion plunge in the BAC curve. Taking the first blood sample on the sharply declining phase would result in an unusually fast "apparent" elimination rate of alcohol. However, such "overshoot" phenomena tend to last only about 35 min after the end of drinking, as shown by drinking experiments in gastric bypass patients [31].

Pre-analytical factors, such as incomplete mixing of plasma and erythrocytes before taking aliquots of blood, differing degree of hemolysis in the two blood samples, differential losses of ethanol by evaporation or salting-out of ethanol caused by excess NaF preservatives during head-space analysis, can also account for variation in elimination rates derived from double blood samples [11, 12]. Analytical errors in the determination of ethanol can also impact on the calculated elimination rates.

It is common knowledge that many drunken drivers have problems with their drinking, and clinically, they might be diagnosed as being alcohol dependent [4, 56]. Support for this comes from the high average BAC of 1.5–1.8 g/l in many countries [24, 44]. Those who drink alcohol to reach a BAC exceeding 3.0 g/l have probably been drinking continuously for several days or weeks [40, 55]. This pattern of chronic drinking is associated with the development of cellular and functional tolerance so that people can appear relatively sober and are sufficiently alert to walk and attempt to drive a motor vehicle [28, 53, 55]. Prolonged heavy drinking also leads to dispositional or metabolic tolerance, which can account for the faster rate of metabolism and give a steeper slope in the post-peak BAC elimination phase [28, 49]. The mechanism underlying this ultra-rapid metabolism of ethanol is generally thought to involve an induction of the CYP2E1 enzymes [22, 30, 54].

The initial BAC in drunken drivers with ultra-rapid metabolism (Table 2) averaged over 4.0 g/l and, in one case, even exceeded 5.0 g/l. The average BAC in deaths attributed to acute alcohol intoxication, according to Jones and Holmgren [26], was 3.6 g/l, and many authorities in forensic medicine consider 4.0 g/l as being sufficient to cause death [32, 52]. But because many drunk drivers have probably been consuming alcohol more or less continuously for several days or weeks, a pronounced tolerance to the depressant effects of alcohol develops [28].

The mean elimination rate of alcohol from blood was 0.33 g l^{-1} h^{-1}, which is more than twice the accepted value of 0.15 g l^{-1} h^{-1} for moderate drinkers after they consumed smaller doses of alcohol [17, 61]. Others have found average alcohol elimination rates of 0.21 g kg^{-1} h^{-1} (SD, 0.05 g kg^{-1} h^{-1}) in a multi-center study with alcoholics during detoxification [12]. Interestingly, the enhanced capacity to metabolize alcohol is not retained indefinitely, and after a period of abstinence, the elimination rate of ethanol returns to values expected for moderate drinking, namely, 0.15 g l^{-1} h^{-1} [30]. In-vitro studies demonstrate a rapid turnover in the microsomal CYP2E1 enzyme after the absence of substrate [10, 41].

The duration of drinking and the dose of ethanol required to boost the activity of the CYP2E1 enzyme have not been established in humans in an unequivocal way [48]. In a classic human drinking study, Zink and Reinhardt [62] allowed volunteers to consume very large quantities of alcohol for 5–10 h, which resulted in a mean BAC of 2.8 g/l (range, 2.3–4.0 g/l). Despite this pattern of heavy drinking, the elimination rates of alcohol from blood averaged only 0.17 g l^{-1} h^{-1} (range, 0.12–0.27 g l^{-1} h^{-1}), and thus, not much different from 0.15 g l^{-1} h^{-1} (range 0.1–0.19 g l^{-1} h^{-1}) observed after a single moderate dose of alcohol [18]. In rats injected with 3 g ethanol per kg of body weight at 9:00 AM each day for 23 consecutive days, the elimination rate of ethanol from the blood was increased by between 19 and 27% compared with control rats injected with saline [19]. These two studies (humans and rats) suggest that a long period of heavy and continuous drinking is necessary for the development of metabolic tolerance and a more rapid elimination rate of alcohol from blood. Alternatively, some people might have a genetic pre-disposition for rapid disposal of ethanol, owing to the pattern of metabolizing enzymes they have inherited [37].

The inter-individual differences in elimination rates of alcohol from blood need to be considered when expert witnesses and others testify in drunk-driving trials about the pharmacokinetics of ethanol [1, 3, 8, 16, 35]. For example, in some countries, the courts want to know the driver's BAC at the time of driving and not at the time of sampling blood, which is usually 30–90 min later. This requires making a back-extrapolation of BAC, which is considered a dubious practice, owing to the many variable factors involved [35, 45]. Sometimes it becomes necessary to translate a person's BAC into the total amount of alcohol consumed, and this calculation also requires making assumptions about the combustion rate of alcohol [3].

With only a single blood sample available from each drunken driver, which is usually the case in forensic situations, the elimination rate of alcohol is unknown. In criminal trials, when beyond a reasonable doubt is required, it is advisable to work with a range of values to give the suspect the benefit of the doubt. Experience from hundreds of controlled drinking experiments has shown that the vast majority of individuals, as well as drunken drivers, eliminate alcohol from the bloodstream at a rate between 0.10 g l^{-1} h^{-1} and 0.25 g l^{-1} h^{-1}. In alcoholics, during detoxification, the elimination rate of alcohol might be considerably faster, as high as 0.35 g l^{-1} h^{-1} in some individuals [12, 22].

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