*A. W. Jones,[1] Ph.D., D.Sc; Å. Norberg,[1] M.D.; and R. G. Hahn,[1] M.D., Ph.D.*

# Concentration-Time Profiles of Ethanol in Arterial and Venous Blood and End-Expired Breath During and After Intravenous Infusion*

**REFERENCE:** Jones AW, Norberg Å, Hahn RG. Concentration-time profiles of ethanol in arterial and venous blood and end-expired breath during and after intravenous infusion. J Forensic Sci 1997;42(6):1088–1094.

**ABSTRACT:** Ethanol (0.40 g/kg) was administered to 13 healthy men by intravenous (i.v.) infusion at a constant rate for 30 min. The concentrations of ethanol in arterial blood (ABAC), venous blood (VBAC), and end-expired breath (BrAC) were measured at 17 exactly timed intervals. Blood-ethanol was determined by headspace gas chromatography and breath-ethanol was measured with a quantitative infrared analyzer (DataMaster). BrAC was multiplied by 2300 to estimate the concentrations of alcohol in blood. During the infusion of ethanol, ABAC exceeded VBAC by about 10 mg/dL on the average and ABAC was also higher than BrAC $\times$ 2300 by about 4 mg/dL on average. When infusion of alcohol ended, ABAC, VBAC, and BrAC were 94.8 $\pm$ 2.06 ($\pm$SE), 84.7 $\pm$ 1.54, and 89.3 $\pm$ 2.10 mg/dL, respectively. The concentrations of alcohol in blood (ABAC and VBAC) and breath decreased abruptly after the administration of alcohol stopped and by 5 min postinfusion, the A-V differences in concentration of ethanol were small or negligible. The mean apparent half-life of the distribution plunge was 7 to 8 min, being about the same for ABAC, VBAC, and BrAC. The disappearance rate of ethanol was 15.5 $\pm$ 0.55 mg/dL/h (mean $\pm$ SE) for arterial blood, 15.2 $\pm$ 0.49 mg/dL/h for venous blood, and 16.3 $\pm$ 0.73 mg/230 L/h for breath; no significant differences were noted ($p > 0.05$). We conclude that A-V differences in the concentration of ethanol exist during the loading phase but are rapidly abolished when the administration of ethanol terminates. In the post-absorptive phase of ethanol kinetics, when alcohol has mixed with the total body water, VBAC exceeds ABAC by about 1–2 mg/100 mL on average.

**KEYWORDS:** forensic science, alcohol, analysis, arterial-blood, breath, venous-blood, A-V difference, pharmacokinetics

Measuring the concentration of a drug in arterial blood provides information about the amount of substance infiltrating the brain, which is important information in studies of drug-induced effects on performance and behavior (1–3). Because routine arterial puncture is not a very practical way of obtaining blood samples for forensic purposes, cubital vein blood has substituted for arterial blood as the specimen for alcohol analysis (4).

The existence of arterial-venous (A-V) differences in the concentrations of ethanol has attracted attention among forensic scientists for two principal reasons. One reason is the phenomenon of acute tolerance to ethanol also known as the Mellanby effect (5,6). The feelings of inebriation and the diminished performance after drinking alcohol are more pronounced on the rising limb as opposed to the falling limb of the BAC-time profile even though the same concentration of ethanol exists in the venous blood (7,8). These observations can be explained, at least in part, by higher concentration of alcohol in arterial blood and therefore brain tissue than in venous blood during the absorption or loading phase prior to equilibration of alcohol with total body water (1,3). During the post-absorptive phase of ethanol kinetics, the concentrations of alcohol in arterial blood and venous blood returning from tissues are much closer (3). What this means is that VBAC and the observed effects of ethanol on performance and behavior are not exactly in phase owing to an ongoing distribution/equilibration process being especially apparent on the rising limb of the BAC-time profile (9).

The second reason for forensic interest in arterio-venous difference stems from the use of breath-alcohol instruments in law enforcement practice (10,11). Breath-tests for alcohol appeared during the 1940s to provide a quick and easy way to estimate the concentration of alcohol in a person's blood (6). The first breath-alcohol analyzers were calibrated for this purpose with a blood/breath factor or ratio which was determined empirically by comparing breath-alcohol and venous blood-alcohol in near simultaneous samples collected during the post-absorptive phase of ethanol metabolism (12). Because the BrAC time course follows more closely ABAC rather than VBAC, breath-tests for alcohol will tend to overstate VBAC whenever marked A-V differences exist, such as during or shortly after drinking when BAC is still rising. The implications of A-V differences have been much discussed and debated when results of breath-alcohol testing are used for prosecution of drinking drivers. However, very few empirical studies have been done to address the scientific issues involved and to shed light on the magnitude and duration of A-V differences in concentrations of ethanol (10,11).

The present investigation expands on earlier studies dealing with arterio-venous differences in alcohol concentration and also includes measurements of alcohol in end-expired breath. A moderate dose of alcohol was administered to healthy volunteers by constant rate i.v. infusion and gas chromatography was used to determine the concentrations of ethanol in near simultaneously taken samples of blood from a radial artery and a cubital vein.

[1]Department of Forensic Toxicology, University Hospital, Linköping and Departments of Anesthesiology, Southern Hospital, Stockholm, and Huddinge University Hospital, Huddinge, Sweden.

*Paper presented at the 47th Annual Meeting of the American Academy of Forensic Sciences, Seattle, Washington, 1994.

Received 13 Sept. 1996; and in revised form 15 Jan. 1997; accepted 24 Feb. 1997.

Copyright © 1997 by ASTM International

## Materials and Methods

### *Subjects and Conditions*

Thirteen healthy men with mean age 31 ± 3 y (±SD) and mean body weight 77 ± 6 kg were recruited for this study as paid volunteers. Written informed consent was obtained from each subject and the study protocol was approved by the ethics review board at the Huddinge University Hospital, Sweden. All the subjects were accustomed to moderate drinking and some occasionally smoked cigarettes although not during the experiments. Each subject participated in two experiments and 0.40 g ethanol/kg body weight was administered once in the morning at 8.30 a.m. and again in the afternoon the same day at 1.30 p.m. In a randomized order either in the morning or the afternoon sessions, the hand on the arm used for sampling blood was either heated to produce vasodilation or cooled to cause vasoconstriction because we also wanted to investigate whether changes in blood flow caused by heating or cooling might influence the A-V differences in ethanol concentration (13). In the present article, we report only the results from the control sessions without heating or cooling the hand and with the main focus on forensic science aspects of A-V differences in concentration of alcohol.

### *Experimental Procedure*

The subjects arrived at the laboratory at about 8.00 a.m. after an overnight fast. Indwelling catheters were inserted into a radial artery at the wrist of one arm and into a large cubital vein on the same forearm to permit sampling of arterial and venous blood, respectively. A catheter was inserted into a cubital vein on the opposite arm and connected to an IVAC model 560 infusion pump (San Diego, CA). Ethanol (10% w/v in glucose) in a dose of 0.40 g per kg body weight was administered at a constant rate over 30 min. The exact concentration of ethanol in these infusion solutions was verified by gas chromatographic analysis (14).

### *Blood-Alcohol Analysis*

Samples of venous blood and arterial blood were taken at 17 exactly timed intervals of 0, 10, 20, 30, 35, 40, 45, 50, 55, 60, 75, 90, 120, 150, 180, 210, and 270 min from the start of infusion. The samples of blood were drawn into 5 mL Vacutainer tubes (Becton Dickinson, New Jersey) containing NaF (20 mg) and sodium heparin (143 units) as preservatives. The catheter tubing was flushed with a few drops of heparin-saline solution to prevent coagulation between taking successive samples.

The concentration of alcohol in blood was determined by headspace gas chromatography as described in detail elsewhere (14). Aliquots (100 μL) of the well mixed whole blood were removed from the Vacutainer tubes and immediately diluted 11-fold with n-propanol (8 mg/dL) as an internal standard. The diluted samples were ejected directly into glass vials (22 mL volume) which were made air-tight with rubber stoppers and crimped-on aluminum caps in preparation for headspace analysis. The chromatographic column was made of stainless steel (2 m by 3 mm ID) which was packed with Carbopack C (0.2% Carbowax 1500 on Carbopak 80–100 mesh) as the stationary phase. The within-run precision of this method (standard deviation) was 0.8 mg/dL at a mean BAC of 100 mg/dL which corresponds to a coefficient of variation of less than 1% indicating high analytical precision (14). In most instances, only a single determination of blood-ethanol was made at each sampling point.

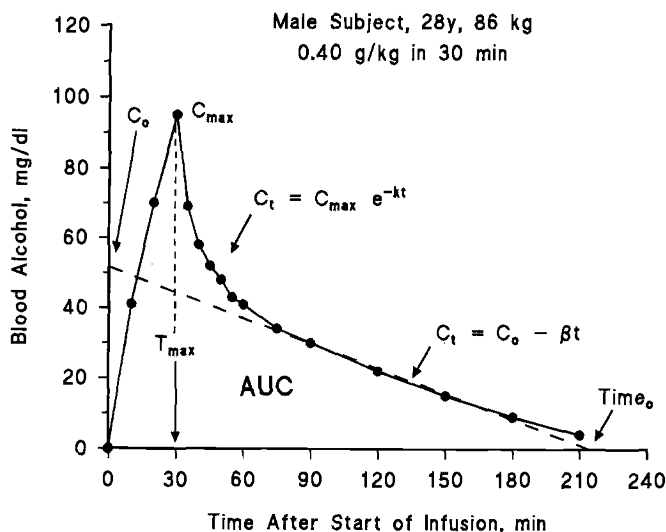



FIG. 1—*Representative concentration-time profile of alcohol in venous blood after intravenous infusion of alcohol (0.40 g/kg) over 30 min. The blood-alcohol parameters of interest are indicated on this plot.*

### *Breath-Alcohol Analysis*

The concentration of alcohol in end-expired breath was determined with a DataMaster infrared analyzer (National Patent Analytical Systems Inc., Mansfield, Ohio). This instrument is widely used for evidential breath-alcohol testing of motorists and replicate determinations of the BrAC can be made every 1–2 min. The precision of a single determination of breath-alcohol was determined by making a large number of duplicate determinations and the standard deviation was 1.2 mg/230 L (Norberg et al. unpublished work). However, in most experiments, only a single breath-alcohol measurement was made at each sampling time.

### *Evaluation of Results*

For each subject, the individual blood-ethanol and breath-ethanol profiles were plotted and evaluated by defining a set of summary measures to characterize the time course of ethanol in the body (15,16). Peak BAC (arterial and venous) and BrAC were noted and the rate of disappearance of alcohol from blood and breath (β-slope) was derived from the pseudolinear elimination part of the curves that developed about 60–90 min after ending the infusion. The apparent volume of distribution of ethanol ($V_d$) was calculated empirically as the dose (0.4 g/kg) divided by the concentration of alcohol in blood at time zero ($C_0$). The latter parameter corresponds to the y-intercept of the concentration-time regression equation and the x-intercept therefore reflects the time required to eliminate the dose of alcohol from the body ($time_o$) disregarding the curvilinear part of curve starting at BAC of 5–10 mg/dL or less. The areas under the concentration-time profiles (AUC) were calculated by the trapezoidal rule (17). Finally, the apparent rate of equilibration of ethanol between the blood and other body organs and tissue after the infusion ended was determined from the slope (k) of the diffusion plunge by fitting a first-order rate equation (17). The apparent half-life of equilibration was derived as $t^1/_2 = 0.69/k$, where k corresponds to the first-order rate constant. Because of large inter-subject variations, curve fitting to the post-infusion diffusion plunge was done using the average curves for all 13 subjects.

## Results

### *Concentration-Time Profiles of Ethanol after Intravenous Infusion*

Figure 1 shows a representative example of a blood-alcohol profile after i.v. infusion with the various pharmacokinetic parameters defined. Figures 2–4 show the individual concentration-time profiles as well as the average curves for arterial-blood, venous-blood and breath-alcohol. Large inter-individual variations were evident despite the highly standardized conditions used to administer alcohol, that is, intravenous infusion of a moderate dose adjusted for differences in body weights. Three phases can be identified in the concentration-time profiles after i.v. infusion. First, the ABAC, VBAC, and BrAC increased steadily during the 30 min infusion period. The second phase begins at the end of the infusion when the alcohol equilibrates throughout all the body fluids and tissues. During this phase, the blood and breath-alcohol concentrations decease abruptly in an exponential manner which lasted for about

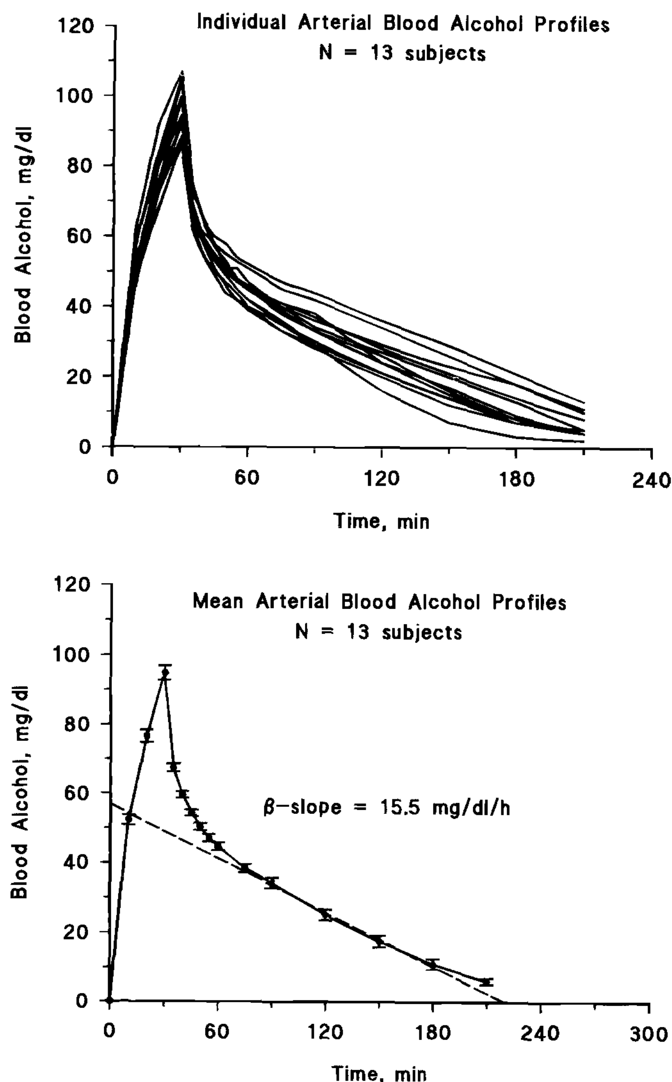
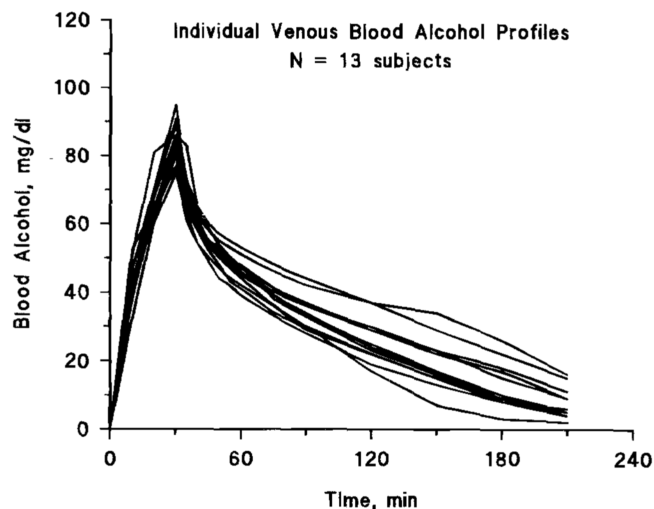



FIG. 2—*Individual concentration-time profiles of alcohol in arterial blood for 13 subjects. The blood was drawn from a radial artery at 17 exactly timed intervals during and after intravenous infusion of 0.40 g/kg. Also shown is the average concentration-time profile with mean ± SE plotted at each sampling time.*



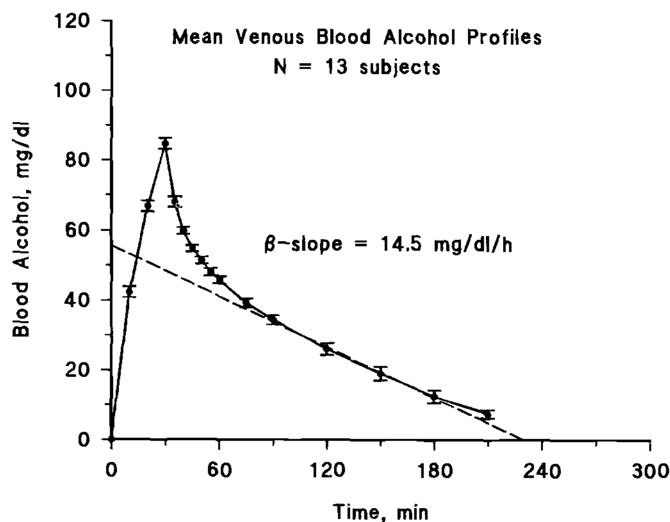




FIG. 3—*Individual concentration-time profiles of alcohol in venous blood for 13 subjects. The blood was drawn from an antecubital vein at 17 exactly timed intervals during and after intravenous infusion of 0.40 g/kg. Also shown is the average concentration-time profile with mean ± SE plotted at each sampling time.*

60–90 min. During the third phase, the concentrations of ethanol in blood and breath decrease in a rectilinear manner until the concentrations reach low levels (<10 mg/dL). The inter-subject variation (coefficient of variation) in key pharmacokinetic parameters and tests of statistical significance for ABAC, VBAC, and BrAC are shown in Table 1.

### *Arterio-Venous Differences in Concentration of Alcohol*

Figure 5 (upper trace) plots differences between arterial BAC and venous BAC as a function of time after starting the infusion of alcohol. During the loading phase ABAC exceeds VBAC for all subjects by about 10 mg/dL on the average ($p < 0.001$). At the end of infusion, the ethanol equilibrates rapidly across the capillary membranes and 5 min later the A-V differences were small or negligible. Late into the post-absorptive phase the VBAC now exceeded ABAC by 1–5 mg/dL at most sampling points but with variations evident for individual subjects.

Figure 5 (middle) is a plot of difference for the concentrations

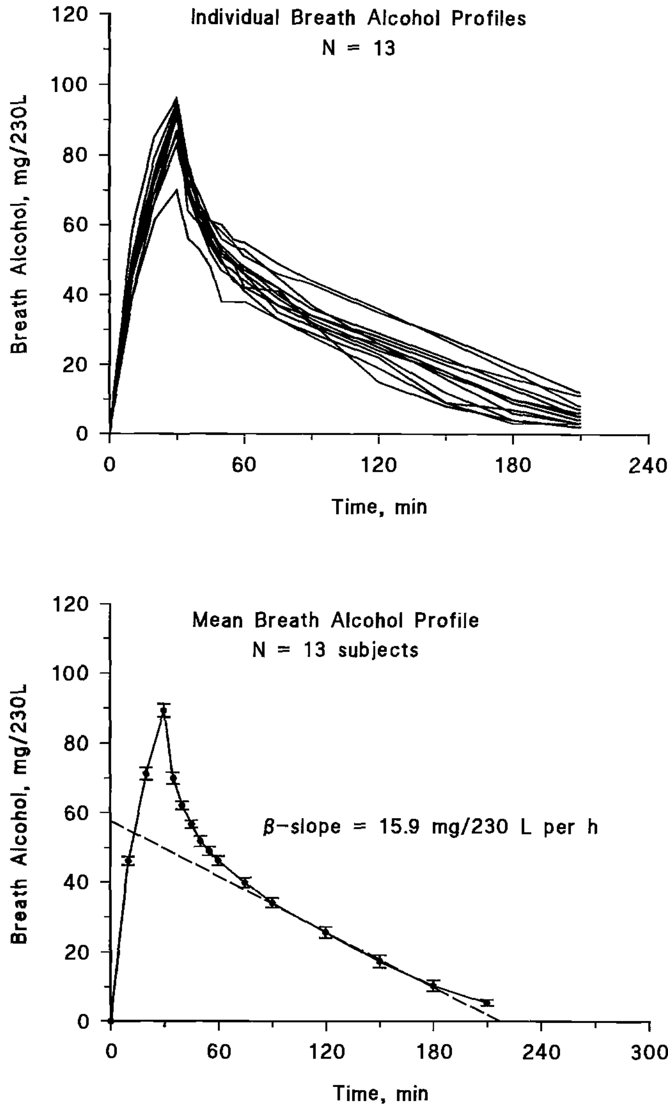



FIG. 4—*Individual concentration-time profiles of ethanol in breath (×2300) from 13 subjects. The end-exhaled breath was analyzed with a quantitative infrared analyzer (DataMaster) at 17 exactly timed intervals during and after intravenous infusion of 0.40 g/kg. Also shown is the average concentration-time profile with the mean ± SE plotted at each sampling point.*

of alcohol in arterial blood and the estimated BAC derived as BrAC × 2300. The differences ABAC-BrAC were less than ABAC-VBAC (Fig. 6 upper plot) during the loading phase and on ending the infusion the ABAC-BrAC difference was rapidly diminished.

Figure 5 (bottom trace) shows a plot of the differences in breath-alcohol concentration (×2300) and VBAC as a function of time after starting the infusion. The estimated BAC values (BrAC × 2300) exceed VBAC during the infusion period and for some time thereafter. During the post-absorptive phase VBAC now exceeded the values estimated indirectly from the analysis of end-expired breath.

### *Comparing Concentrations of Alcohol in Blood and Breath*

Figure 6 shows a plot of venous BAC and BrAC in one subject with a logarithmic ordinate scale so that the same units of alcohol concentration can be used (mg/L) for both breath and blood. Also shown are the BrAC concentration-time profiles resulting when breath-alcohol is multiplied by arbitrary factors of 100, 200, and 2000. These manipulations bring the BrAC profiles successively closer to the venous BAC profile. However, it is obvious that the closeness of agreement between them depends on the particular blood/breath factor chosen to calibrate the breath-alcohol analyzer.

## Discussion

Two comprehensive review articles by Chiou (18,19) discussed the implications of A-V differences in clinical pharmacokinetics and toxicology and the need to consider the blood-sampling site when interpreting drug concentrations. Chiou called for more detailed studies of this topic and here we respond with a study of ethanol pharmacokinetics in arterial and venous blood and end-expired breath. The basic principles governing absorption, distribution, and elimination of alcohol as well as the existence of A-V differences in ethanol concentration were demonstrated in animal studies already in the 1940s (20,21). This early work was confirmed by Gostomzyk et al., (22) who administered alcohol (0.8 g/kg) to rabbits by i.v. infusion for 5 to 25 min. The peak ABAC (brachial artery) was compared with VBAC (femoral vein) and the A-V difference was maximum at the end of infusion. The faster the rate of alcohol infusion, the greater the A-V differences observed. Levitt et al. (23) recently discussed the need to consider blood sampling site, A-V differences and ratios of blood flow to tissue

TABLE 1—*Comparison of blood-alcohol parameters derived from analysis of arterial blood (radial artery), venous blood (cubital vein), and end-expired breath. The BrAC was multiplied by a factor of 2300:1 to make comparisons with blood-alcohol concentration for more meaningful results. Values shown are mean ± SE for N = 13 healthy male volunteers and statistical analysis was by one-way analysis of variance; CV = coefficient of variation (SD/mean) × 100. AUC = area under the curve.*

| Specimens analyzed | Peak EtOH Conc. mg/dL | β-slope mg/dL/h | $C_0$ mg/dL | $V_d$ l/kg | $time_0$ min | AUC mg/dL × min |
|---|---|---|---|---|---|---|
| Arterial Blood | 94.7 ± 2.0* | 15.4 ± 0.56† | 58 ± 1.8† | 0.695 ± 0.021† | 223 ± 7.2† | 6875 ± 233† |
| (ABAC) | CV = 7.6% | CV = 13.1% | CV = 11.1% | CV = 10.9 | CV = 11.6% | CV = 12.2% |
| Venous Blood | 84.7 ± 1.5 | 15.2 ± 0.45 | 59 ± 1.7 | 0.689 ± 0.019 | 227 ± 7.3 | 6722 ± 227 |
| (VBAC) | CV = 6.4% | CV = 16.7% | CV = 10.3% | CV = 9.9% | CV = 11.6% | CV = 12.1% |
| End-expired Breath | 88.2 ± 2.1 | 16.3 ± 0.73 | 60 ± 1.9 | 0.674 ± 0.021 | 220 ± 7.7 | 6791 ± 237 |
| (BrAC) | CV = 8.6% | CV = 16.1% | CV = 11.4% | CV = 11.2% | CV = 12.6% | CV = 12.5% |

*Significantly higher than VBAC and BrAC, $p < 0.001$.
†Not significantly different from VBAC and BrAC, $p > 0.05$.

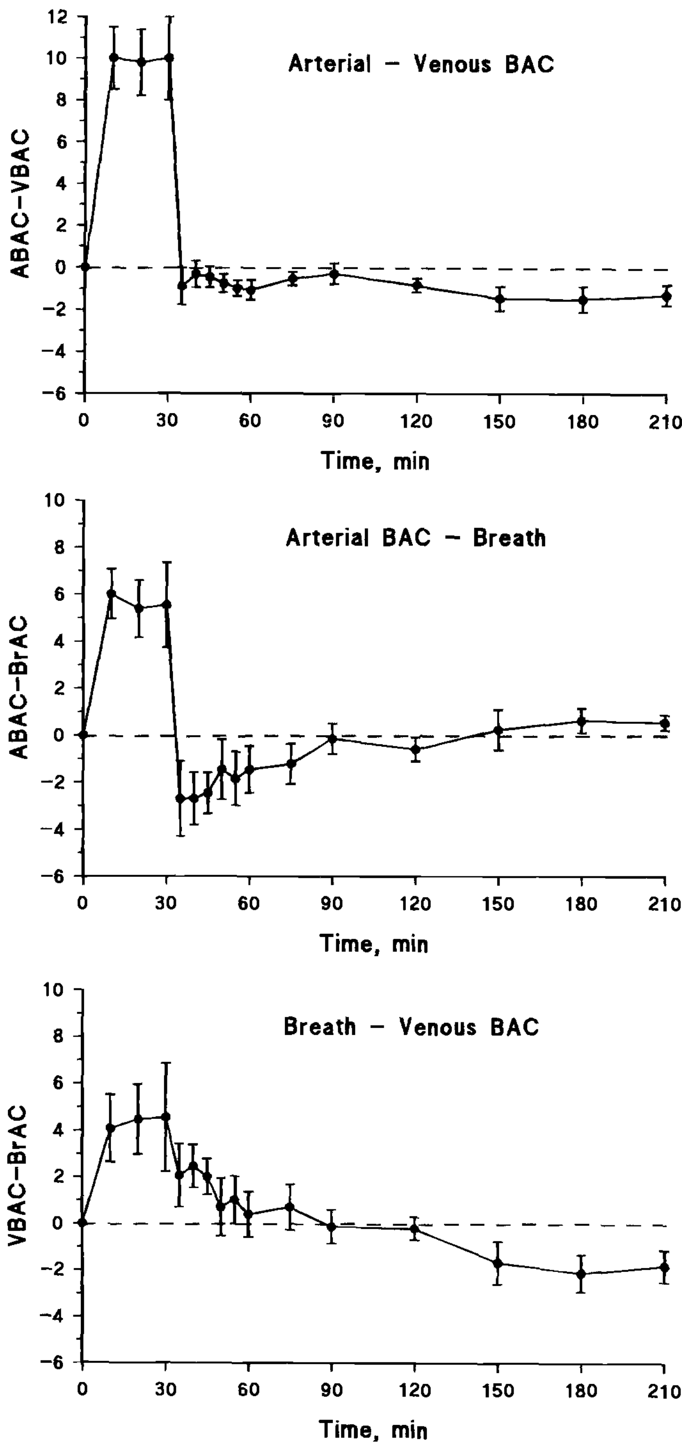



FIG. 5—*Differences in the concentrations of ethanol in arterial and venous blood (upper trace), arterial-blood and breath (middle trace) and breath-alcohol and venous blood-alcohol (bottom trace). Mean curves ± SE are shown as a function of time for 13 subjects at 17 exactly timed intervals during and after intravenous infusion of 0.40 g/kg.*

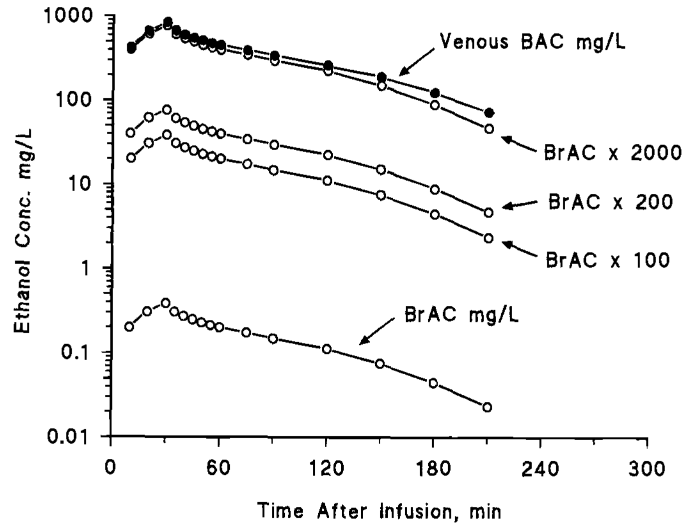



FIG. 6—*Comparison of venous blood and breath alcohol concentrations with the use of a logarithm ordinate scale so that the same units of concentration could be used for both media (mg/L) The breath-alcohol profile is shown after multiplying each of the BrAC results by 100, 200, and 2000 which were taken as the presumed blood:breath factors.*

perfusion in studies of ethanol pharmacokinetics especially during the rising and declining arms of the BAC curve.

Much less work has been done to investigate A-V differences of alcohol in humans probably because of the need to insert and maintain an indwelling arterial catheter for sampling blood at regular intervals. However, an early study by Forney et al. (24) compared the concentrations of alcohol in blood from radial artery and cubital vein in two volunteers who drank 1.05 g ethanol/kg in 30 min. Specimens of blood and breath were obtained at 30 min intervals for 105 min after starting drinking. One subject reached a peak ABAC early after the end of drinking and the A-V difference was 37 mg/dL (26%), decreasing to 8% by 15 min postdrinking and was negligible at 30 min. The other subject absorbed alcohol much more slowly and the A-V differences persisted for as long as alcohol was being absorbed, being 66% at the end of drinking dropping to 23% after 45 min and at the last sampling time (105 min) the VBAC exceeded ABAC.

Martin et al. (25) reported the most detailed investigation of A-V differences in humans and their protocol also included the analysis of alcohol in exhaled breath. BrAC was determined with a chemical oxidation method (Alcolinger) similar in principle to the Breathalyzer model 900 widely used in the US. The volunteers drank 0.5, 0.75, 1.0, or 1.25 g/kg body weight and the concentrations of alcohol in blood from cubital vein, brachial artery, and breath were measured at various times after drinking. A-V differences in the concentration of ethanol reached were as much as 30 mg/dL during the absorption phase and BrAC × 2100 was closer to ABAC than VBAC.[2] The authors conclude that BrAC is a better predictor of ABAC than VBAC during the absorption phase of ethanol pharmacokinetics (25). Concentrations of ethanol in arterial and venous blood were compared in trauma patients (26) and during the post-absorptive phase of ethanol metabolism very good agreement was noted. Moreover, the rate of disappearance of alcohol (β-slope) was about the same regardless of whether arterial or venous blood samples were analyzed (26).

The magnitude of the A-V differences in our study during the loading phase was less than those observed in the earlier investigations by Forney et al. (24) and Martin et al. (25). However, these workers allowed the volunteer subjects to drink the dose of alcohol and we gave the alcohol by a constant rate i.v. infusion. It seems likely that the route of administration of a drug is also important to consider when evaluating the impact

[2]Note that the study by Martin et al. (25) made use of a 2100:1 blood-breath factor as is usual with the Breathalyzer 900 instrument, whereas our study with the Datamaster used a 2300:1 factor.

of A-V differences during the absorption or loading stage of ethanol pharmacokinetics. A-V differences can be expected whenever the rate of absorption from the stomach or infusion into a vein occurs faster than the rate of equilibration between blood and tissue water across the sampling site, here the skeletal muscles of the arm. Clearly, A-V differences in ethanol content should be more pronounced for those organs and tissue with a relatively low blood flow per unit mass of tissue fluid. When the flow of blood is large in relation to the mass of tissue, such as for kidney or salivary glands, the A-V difference in concentration of alcohol should be negligibly small (27). The maximum A-V differences can be expected in resting skeletal muscle tissue and we report here a mean value of 10 mg/dL when a dose of 0.40 g/kg was given by intravenous infusion over 30 min; higher doses, more rapid rates of infusion or other routes of administration might produce more pronounced A-V differences.

Drugs that can easily diffuse through capillary walls to reach the extravascular tissues will show A-V differences (28). Ethanol is a good example of a drug not metabolized in skeletal muscle tissue to any measurable extent and during the loading phase, ethanol is readily taken up by the sampling tissue. This leads to a loss of drug from the arterial blood so that the concentration in venous blood leaving the tissue will be lower than in the arterial blood entering the tissue (18). When the uptake of ethanol by the sampling tissue ends, the A-V differences are abolished and our results show that this happens within 5 min after ending the infusion (Fig. 5). We observed a mean A-V differences of 10 mg/dL (maximum 28 mg/dL in one subject) during infusion of alcohol but this was reduced considerably or eliminated altogether by 5 min postinfusion. This indicates a fairly rapid transfer of ethanol from skeletal muscle tissue into the venous blood as might be expected for low-molecular weight hydrophilic substances moving freely between intra- and extra-cellular compartments. On ending the infusion of ethanol, the VBAC, ABAC, and BrAC decreased abruptly with an apparent $t_{1/2}$ of 7–8 min although this reflects both distribution and elimination processes. At about 90 min post-infusion, VBAC tended to be higher than ABAC ($p < 0.05$) for the remainder of the concentration-time profile by 1–2 mg/dL on average (maximum 8 mg/dL in one subject).

Comparing breath-alcohol concentration (BrAC) with VBAC or ABAC is not an easy task because of the need to assume a certain breath-to-blood conversion factor to obtain meaningful results. The agreement will obviously depend on the magnitude of the blood/breath factor as illustrated by the plots in Fig. 6 which underscore the impossibility of obtaining unbiased estimates of ABAC and VBAC throughout the entire concentration-time profiles when one fixed blood/breath conversion factor is used. The conversion factor or blood/breath ratio of alcohol generally accepted for medicolegal purposes is 2000:1 in France and Austria, 2100:1 in US, Canada, and Sweden and 2300:1 in Great Britain and Netherlands. A blood/breath ratio of 2300:1 gives excellent agreement between breath-alcohol and venous and arterial BAC in the postabsorptive phase. Accordingly, the use of a fixed ratio of 2100:1 would tend to underestimate BAC during the postabsorptive period. The analysis of venous blood samples gives a minimum estimate of the exposure of the brain to alcohol which is important to remember when alcohol-induced impairment of body functions is being considered. This follows because the effects of alcohol on performance and behavior are more closely correlated with the concentration reaching the brain tissue as reflected in ABAC and BrAC.

Inter-relationships between venous, arterial and breath-alcohol concentrations have been discussed at length in the scientific literature, particularly in connection with the use of evidential breath-alcohol testing in law enforcement. However, relatively few studies have addressed this question empirically and information is sparse concerning the impact of blood-sampling site and A-V differences in clinical pharmacokinetics and therapeutic drug monitoring (18,19). The critical threshold limits of blood and breath-ethanol concentrations are defined by statute, e.g., 0.1 g% w/v or 0.1 g/210 L breath for driving in many US states. However, the sampling site for drawing blood is not specified which suggests that venous, capillary, and arterial BAC are acceptable for legal purposes. The current policy of reporting BrAC directly without bothering to convert to BAC avoids the need to consider variability in blood-breath ratios and the existence of A-V differences in concentration of alcohol.

*Acknowledgment*

This work was supported in part by a grant from the Forensic Science Center, Linköping University, Linköping, Sweden.

## References

1. Harger RN, Hulpieu HR, Lamb EB. The speed with which various parts of the body reach equilibtration in the storage of ethyl alcohol. J Biol Chem 1937;120:689–704.
2. Forney RB, Hulpieu HR, Harger RN. The levels of alcohol concentration in brain, peripheral blood and heart blood ten minutes after oral administration. J Pharmacol 1950;98:8–9.
3. Sunahara GL, Kalant H, Schofield M, Grupp L. Regional distribution of ethanol in the rat brain. Can J Physiol Pharmacol 1978;56:988–92.
4. Garriott JC. (editor) Medicolegal aspects of alcohol. 3rd edition, Lawyers & Judges Publishing Co, Tucson, 1996;1–526.
5. Mellanby E. Alcohol; Its absorption into an disappearance from the blood stream under different conditions. British medical research council special report, Series no 31, HMSO, London, 1919.
6. Jones AW. Measuring alcohol in blood and breath for forensic purposes; A historical review. Forensic Sci Rev 1996;8:14–44.
7. Martin CS, Earleywine M. Ascending and descending rates of change in blood alcohol concentrations and subjective intoxication rates. J Sub Abuse 1990;2:345–52.
8. Martin CS, Moss HB. Measurement of acute tolerance to alcohol in human subjects. Alcoholism Clin Exp Res 1993;17:211–6.
9. Gumbleton M, Oie S, Verotta D. Pharmacokinetic pharmacodynamic (PK-PD) modelling in non-steady-state studies and arterio-venous drug concentration differences. Br J Clin Pharmacol 1994;38:389–400.
10. Jones AW. Enforcement of drink driving laws by use of "per se" legal alcohol limits; Blood and/or breath concentration as evidence of impairment. Alc Drugs Driving 1988;4:99–112.
11. Jones AW. Physiological aspects of breath-alcohol measurements. Alc Drugs Driving 1990;6:1–25.
12. Harger RN, Forney RB, Barnes HB. Estimation of the level of blood alcohol from analysis of breath. J Lab Clin Med 1950;36:306–18.
13. Norberg Å, Jones AW, Hahn RG. Pharmacokinetics of ethanol in arterial and venous blood and in end-expired breath during vasoconstriction and vasodilation. Am J Therap 1995;2:954–61.
14. Jones AW, Schuberth J. Computer-aided headspace gas chromatography applied to blood-alcohol analysis; Importance of on-line process control. J Forensic Sci 1989;34:1116–27.
15. Jones AW. Disappearance rate of ethanol from blood in human subjects; Implications in forensic toxicology. J Forensic Sci 1993;38:104–18.
16. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. Brit Med J 1990; 300:230–5.
17. Roland M, Tozer TN. Clinical pharmacokinetics; Concepts and applications. Lea & Febiger, Philadelphia, 2nd edition, 1989.

18. Chiou WL. The phenomenon and rationale of marked dependence of drug concentration on blood sampling site (Part 1). Clin Pharmacokinet 1989;17:175–99.
19. Chiou WL. The phenomenon and rationale of marked dependence of drug concentration on blood sampling site (Part II). Clin Pharmacokinet 1989;17:275–90.
20. Haggard HW, Greenberg LA, Rakieten N. Studies on the absorption, distribution, and elimination of alcohol. VI The principles governing the concentration of alcohol in the blood and the concentration causing respiratory failure. J Pharmacol Exp Therap 1940; 69:252–65.
21. Haggard HW, Greenberg LA, Lolli G. The absorption of alcohol with special reference to its influence on the concentration of alcohol appearing in the blood. J Stud Alc 1941;1:684–726.
22. Gostomzyk JG, Dilger B, Dilger K. Untersuchungen über die arteriovenöse Differenz der Alkoholkonzentration im Blut und ihre Beziehung zum Alkoholgehalt des Gehirns. Z Klin Chem Klin Biochem 1969;7:162–6.
23. Levitt MD, Furne J, DeMaster EG. Magnitude, origin, and implications of the discrepancy between blood ethanol concentrations of tail vein and arterial blood of the rat. Alcohol Clin Exp Res 1994;18:1237–41.
24. Forney RB, Hughes FW, Harger RN, Richards AB. Alcohol distribution in the vascular system; Concentrations of orally administered alcohol in blood from various points in the vascular system, and in rebreathed air, during absorption. J Stud Alc 1964;25:205–17.
25. Martin E, Moll W, Schmid P, Dettli L. The pharmacokinetics of alcohol in human breath, venous and arterial blood after oral ingestion. Eur J Clin Pharmacol 1984;26:619–26.
26. Kleemann WJ, Seibert M, Tempka A, Wolf M, Weller JP, Tröger HD. Arterielle und venöse Alkoholelimination bei 10 polytraumatisierten Patienten. Blutalkohol 1995;32:162–73.
27. Coleman TG, Manning RD, Norman RA, Guyton AC. Dynamics of water-isotope distribution. J Appl Physiol 1972;227:1371–5.
28. Chiou WL, Lam G. The significance of the arterial-venous plasma concentration differences in clearance studies. Int J Clin Pharm Ther Tox 1982;20:197–203.

Additional information and reprint requests:
A. Wayne Jones, Ph.D., D.Sc.
Department of Forensic Toxicology
University Hospital
581 85 Linköping
Sweden