Impact of Trauma, Massive Blood Loss and Administration of Resuscitation Fluids on a Person's Blood-Alcohol Concentration and Rate of Ethanol Metabolism

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ABSTRACT

Excessive drinking and drunkenness are tightly linked to many types of intentional and unintentional injuries involving trauma and blood loss, which often necessitate emergency medical intervention. This article considers the impact of trauma, massive blood loss, and the administration of life-saving replacement fluids on a person's blood alcohol concentration (BAC) and rate of ethanol metabolism. Both German and English language journals were reviewed and results from animal experiments, human studies, and actual victims of trauma undergoing life-saving treatment were considered. If trauma-related bleeding occurs when some ingested alcohol remains unabsorbed in the stomach, then under these circumstances continued absorption into portal venous blood is delayed, owing to altered splanchnic circulation. Hemodilution caused by administration of replacement fluids has only minimal effects on a preexisting BAC, because ethanol distributes into the total body water (TBW) compartment, which represents 50-60% of body weight. After hypovolemia there is a transfer of fluids from tissue compartments into the blood, which becomes more like plasma in composition with lower hematocrit and hemoglobin content. Unless the trauma or emergency treatment impedes hepatic blood flow, the rate of ethanol metabolism is not expected to differ from normal values, namely 0.10-0.25 g/L/h (0.01-0.025 g% per h). If ethanol is fully absorbed and distributed in all body fluids and tissues, neither massive blood loss nor administration of resuscitating fluids is expected to have any significant effect on a preexisting BAC or the rate of ethanol metabolism. *Acad Forensic Pathol.* 2016 6(1): 77-88

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INTRODUCTION

Heavy drinking and drunkenness are tightly linked to many types of accidents and trauma injuries that require emergency medical intervention (1-3). After appreciable blood loss (>1000 mL), the injured person enters a state of hypovolemic shock, which requires the administration of replacement fluids as part of life-saving medical treatment (4). The question of whether trauma injuries, massive blood loss, and/or replacement fluids alter a person's blood alcohol concentration (BAC) often arises during forensic investigations of living and deceased persons.

Many epidemiological studies verify that drunk drivers are overrepresented in road traffic crashes and most nations enforce punishable BAC limits for driving a motor vehicle. These limits vary from 0.20-0.80 g/L (0.02-0.08 g%) in different countries (5). Statistics show that between 20-50% of drivers killed in crashes had been drinking alcohol and that their BAC at autopsy was above the statutory alcohol limit for driving (6-8). This has legal ramifications when culpability for the crash is investigated and when insurance claims are made because compensation to next of kin or third parties might be null and void if the driver's BAC was above the statutory alcohol limit for driving (6, 9).

Accurate, precise, and specific analytical methods are available for determination of ethanol in blood samples by gas-liquid chromatography (GLC), which is the gold-standard method used in forensic and toxicology laboratories worldwide (10). When ethanol is determined in blood or other biological fluids, the composition of the specimen, especially the water content, is important to consider. The composition of blood samples taken from victims of trauma might depend on the type of traumatic event, volume of blood lost, and emergency medical treatment, such as administration of resuscitation fluids (11, 12). The question of whether trauma injuries, associated blood loss, or any emergency life-saving treatment might have altered a person's BAC often arises during investigations of road traffic crashes.

This article reviews publications dealing with trauma, massive blood loss, and administration of resuscitation fluids and how these impact on a person's BAC and rate of ethanol metabolism. The body's physiological response to trauma, blood loss, and administration of replacement fluids are discussed in relation to results of blood ethanol analysis. Questions about the reliability of forensic BAC measurements often occur when culpability for a road traffic crash is investigated by police authorities and when insurance claims are made.

Ethanol in the Body

The disposition and fate of ethanol in the body has been studied extensively since the 1930s after the pioneering work by Erik M.P. Widmark from University of Lund, Sweden (13, 14). Accordingly, much is already known about the pharmacokinetics and pharmacodynamics of ethanol in humans under different drinking conditions in both males and females (15, 16). After consumption of alcoholic beverages, the ethanol they contain is rapidly absorbed from the stomach and upper part of the small intestine (duodenum and jejunum), to reach the portal venous blood (17). The speed of absorption of ethanol depends on gastric emptying, which in turn is influenced by presence of food in the stomach, blood glucose content, use of certain prescription drugs, and any surgery to the gut, such as gastric bypass operation, as reviewed elsewhere (15, 18).

Hundreds of controlled ethanol dosing studies verify that peak BAC (C_{max}) is reached within 5-120 minutes after end of drinking, with a mean of about 60 minutes (19). The times required to reach C_{max} observed in controlled laboratory experiments are not expected to be much different from real-world drinking conditions, such as when people attend bars or restaurants and drink alcoholic beverages at intervals over several hours (20). Accordingly, if the trauma and blood loss occurs later than two hours after end of drinking, negligible amounts of alcohol remain unabsorbed in the stomach at the time of the trauma.

Ethanol has a low molecular weight (46.05 g/mol), is uncharged at physiological pH, and does not bind to plasma proteins or other blood constituents (14). This means that after drinking alcoholic beverages, ethanol distributes into the total body water (TBW) compartment (21). The TBW compartment depends on a person's age, gender, and degree of adiposity. For nonobese individuals, the TBW corresponds to 50-60% of body weight, with women having less body water than men (22, 23). The speed of equilibration of ethanol between the blood and other body organs and tissue depends on the ratio of blood flow to tissue mass (17).

According to textbooks in medical physiology, the volume of blood in an adult is approximately 5-8% of body weight, which corresponds to 3.5-5.6 L for a person weighing 70 kg. The volume of blood is therefore considerably less than TBW, which amounts to 35-42 L for a 70 kg person. There is a quantitative relationship between a person's BAC and the amount (grams) of ethanol absorbed and distributed in all body fluids and tissues (16). From knowledge of a person's body weight and BAC, the quantity of alcohol in all body fluids and tissues can be calculated using Widmark's equation (15, 24).

The oxidative metabolism of ethanol occurs primarily in the liver (95-98%) and only a small fraction of the dose consumed (2-5%) is excreted unchanged via the kidney (with urine) or exhaled in breath (17). Based on results from hundreds of controlled drinking experiments, the mean rate of ethanol elimination from blood is 0.15 g/L/h (0.015 g% per h) with a range from 0.1-0.25 g/L/h (0.01-0.025 g% per h) in the vast majority of people (25). These elimination rates of ethanol from blood correspond to disposal of 0.07-0.18 g/kg/h (mean 0.10 g/kg/h) by the whole body. The rate of elimination of ethanol from blood is faster in chronic heavy drinkers, owing to induction of the hepatic metabolizing enzyme CYP2E1 (26). In alcoholics during detoxification, the mean elimination rate was 0.22 g/L/h (0.022 g% per h) with a maximum of 0.36 g/L/h (0.036 g% per h) (27).

Analytical Aspects

The determination of ethanol in blood and other biological specimens is accomplished with a high degree of accuracy, precision, and specificity by GLC methods of analysis (28, 29). The ethanol content of plasma and serum are approximately 10-15% higher than whole blood, owing to differences in water content (30). Studies have shown that the mean plasma/whole blood distribution ratio of ethanol is about 1.15:1, with a range from 1.10-1.20:1 (31). A blood sample taken after hemorrhagic shock is expected to be more like plasma in composition, with a higher water content, a lower hemoglobin content and a lower hematocrit, owing to loss of red cells (32, 33).

Women have slightly less water in blood than men, owing to gender differences in hematocrit (34). Results from a multicenter study found that the mean water content of whole blood (N = 833) was 78.4% w/w (extreme range 75-83% w/w). In the same study, the mean water content of serum was 90.7% w/w with a range from 87-93% w/w (30). Both hematocrit and hemoglobin content of blood varies with age, gender, and disease states, such as anemia and the normal hematological values are available in clinical laboratory reference books (35). Measuring the hemoglobin content of blood provides a useful biomarker of hemodilution, because hemoglobin only exists in the vascular system (36). After trauma injuries, unless hepatic blood flow is interrupted, there is no evidence that rate of ethanol metabolism is any different from healthy individuals.

The Body's Response to Trauma

The physiological response to trauma injuries depends on several factors, particularly the volume of blood lost from the circulation (hypovolemia). After hemorrhagic trauma, as volume of blood suddenly decreases, the perfusion of vital organs, such as brain and kidneys, is inadequate and they are deprived of oxygen (37). This stimulates the heart to beat faster, and an adrenaline-induced vasoconstriction helps to raise blood pressure and improve the oxygenation of organs and tissues. Depending on the volume of blood lost,

other compensatory mechanisms are activated, such as a decrease in splanchnic circulation, an increase in respiratory rate, and a decrease in urine production (38). Fluid transfer from extravascular compartments into the bloodstream takes place to maintain an adequate circulation. During hypovolemia, patients look pale in the face, they are often confused, suffer from lactic acidosis, and depending on the extent of the trauma, they might become comatose, stop breathing, and die.

After an appreciable blood loss (>1000 mL), this triggers the early stage of hypovolemic shock and life-saving treatment becomes necessary, including administration of intravenous fluids such as sodium lactate, normal saline, and/or various blood substitution products (39). The purpose of the resuscitation fluids is to restore intravascular volume, maintain systolic blood pressure and keep the brain supplied with oxygen (36). However, after blood loss and administration of replacement fluids, the blood becomes more like plasma in composition, with fewer red cells and lower hemoglobin content. The proper diagnosis of hypovolemia requires monitoring blood pressure and heart rate, analysis of blood gases, and assessment of base deficit. The lactate content of the blood furnishes a useful marker of the severity of hypoxia (40, 41).

The principal compensatory mechanism after hemorrhagic shock is the diversion of blood away from nonessential organs, such as the stomach, intestines, and skin into the central compartment to ensure the brain continues to be supplied with oxygen. One consequence of the centralization of blood circulation is that digestion and emptying of stomach contents into the intestines are delayed. The rate of absorption of ethanol from the gut into the portal venous blood after trauma and massive blood loss is also delayed.

The first aid treatment after hemorrhagic shock is to stop further bleeding and administer intravenous fluids (e.g., blood products, saline, Ringer's lactate) to maintain an adequate intravascular volume. This ensures that the heart keeps on pumping and oxygen and glucose are supplied to the brain. The intravenous fluids will, to some extent, dilute blood constituents,

including any alcohol present. However, this effect is transient because resuscitation fluids quickly equilibrate with TBW (50-60% of body weight). The effect of a known volume of replacement fluids on a preexisting BAC is easy to calculate by adding the amount administered (e.g., 5 L) to the total body water (not just blood water) and calculating by how much the BAC is lowered.

Experimental Studies

The effects of massive blood loss and administration of replacement fluids have been investigated in both animals and humans as well as in victims of trauma during life-saving emergency treatment. Most investigations of trauma and blood loss and the influence on BAC and rate of ethanol metabolism have come from Germany and there is a dearth of information on this subject in English language scientific journals.

In an experiment with 11 healthy subjects, 15-20% of their blood volume was removed (0.8-1.35 L) over 35 minutes. Neither blood pressure, heart rate, cardiac output nor metabolic parameters (lactate-to-pyruvate ratio) changed appreciably after this treatment (42). However, there was a marked decrease in the splanchnic blood volume after hemorrhage, which suggests that the splanchnic circulation serves as a blood reservoir under these conditions. When the volume of blood lost is as much as 30-40% of the total volume (~5-6 L), this represents a life-threatening circulatory failure inevitably resulting in death.

Kintz described a man with a life-threatening stab wound who died from the injury despite emergency treatment, which included 3.25 L of intravenous fluids (43). The autopsy BAC was 0.1 g/L and when the assailant was prosecuted, the question arose of how the intravenous fluids might have altered the victim's BAC. Because these fluids rapidly mix with TBW (50-60% of body weight) and not just blood water, the dilution effect was calculated to be approximately 6.5% and at most 10%, depending in part on blood circulation at time of death. The following conclusion was reached:

Considering the relatively small amount of fluid added compared to the mean distribution volume of ethanol in our case, the effect of ante-mortem perfusion can be considered as minimal (43).

In this case it would have been useful to analyze the hemoglobin content of the blood sample from the injured man, because this would have provided information about hemodilution. Hemoglobin only exists in the bloodstream and is a sensitive indicator of dilution (32).

In emergency medicine, intravenous fluids are sometimes administered distal to the vein used for sampling blood, which can result in an appreciable dilution effect if fluids are administered into a vein on the hand and blood for analysis of alcohol is taken from an elbow vein on the same arm (44). Under these circumstances, measuring hemoglobin in the blood sample would allow making an adjustment to BAC to correct for the dilution effect (45).

Kleeman et al. measured elimination rates of ethanol from arterial and venous blood in patients admitted to hospital for treatment of multiple-trauma injuries and massive blood loss (46). The victims of the trauma received life-saving emergency treatment including infusion of large volumes of resuscitation fluids and blood substitutes. Despite this invasive treatment, the elimination rates of ethanol from blood were within the normally expected values for healthy individuals, namely 0.10-0.25 g/L per h or 0.01-0.025 g% per h (25).

Figure 1 shows concentration-time profiles of ethanol in four representative subjects from the above referenced German study of trauma patients. Patient A (31 year-old male) suffered a self-inflicted stab wound in the chest in a suicide attempt and received 1000 mL Ringer's lactate solution at the scene, a further 2000 mL at hospital, and another 2000 mL over the next four hours during surgical intervention. Patient B (33 year-old male) was involved in a road traffic crash and suffered head trauma and appreciable blood loss. During transportation to hospital, 4000 mL plasma substitute were given, although this large volume of fluid had no marked effect on the rate of ethanol elimination from blood. The lack of effect of trauma and

intravenous replacement fluids on metabolism and elimination rate of ethanol from blood was verified in other trauma victims for whom the elimination rate of ethanol ranged from 0.17-0.21 g/L with a mean of 0.18 g/L (46).

In one of the trauma victims, the BAC curve in the postabsorptive phase levelled off, suggesting a slower rate of ethanol metabolism, but the patient subsequently died on the operating table. The apparent slower rate of ethanol metabolism was explained by a decrease in hepatic blood flow in the agonal phase. In another patient, a slower metabolism of ethanol was observed because hepatic circulation was temporarily circumvented for 30 minutes during a surgical procedure. The results of this study of trauma victims, despite massive blood loss and administration of intravenous fluids, provided no evidence of altered rates of ethanol elimination from arterial and venous blood. The authors reached the following conclusion:

Given our results and the existing literature, we feel that retrograde calculations of the BAC can be justified in patients with poly-trauma, despite the small number of patients included in the study. Naturally, the usual forensic criteria have to be taken into account, as well as individual situations (46).

Another German study investigated the relationship between hypovolemic shock and blood alcohol concentrations in rabbits (47). The dose of ethanol (1.0 or 2.0 g/kg) was given either orally or by intravenous infusion and one hour later, when diffusion-equilibration of ethanol was achieved, 30% of the animal's blood volume was withdrawn from an intravenous catheter. Samples of blood were taken repeatedly from the animals over several hours for quantitative determination of ethanol in serum. The authors concluded that:

Hypovolemic shock had none or little influence and did not lead in any way to irregularities of ethanol elimination except for a slight deceleration of the elimination rate per hour (β_{60}) in animals which received the ethanol by intravenous infusion (47).

Figure 1: Blood concentration time profiles of ethanol in venous and arterial blood in four trauma victims patients A, B, D and G, undergoing emergency treatment, which included intravenous administration of resuscitation fluids and blood substitutes. Graphs modified and redrawn from reference (46).

Figure 1 (Continued): Blood concentration time profiles of ethanol in venous and arterial blood in four trauma victims patients A, B, D and G, undergoing emergency treatment, which included intravenous administration of resuscitation fluids and blood substitutes. Graphs modified and redrawn from reference (46).

The results of the study were discussed in relation to presenting forensic evidence in cases of trauma involving massive blood loss, such as in victims of a road traffic crash.

Kaufmann et al. used dogs to investigate the effect of blood loss on changes in BAC and rates of ethanol elimination (48). Animals were given ethanol (3.0 g/kg) by intravenous infusion to reach a peak BAC of ~2.9 g/L and 60 minutes later one group (n = 8) was drained of 30-40% of their total blood volume until blood pressure dropped to 40 mmHg. The other group of animals (n = 8) served as controls. The severity of the hemorrhagic shock was monitored from changes in blood pH, pCO₂, pO₂, lactate, pyruvate and electrolytes. The mean blood alcohol curves in the test and control groups of dogs are shown in **Figure 2**.

The BAC curves were not much different despite the massive removal of blood volume. There seemed to be a small decrease in rate of ethanol elimination, perhaps caused by a diminished blood flow through the liver. However, the slightly higher BACs observed at one, two and three hours after exsanguination might also be explained by transfer of fluid from tissue into the intravascular space and a higher concentration of ethanol because blood is now more like plasma in composition (30).

Ditt and Schulze allowed healthy male subjects to drink alcohol over two hours until they reached BACs ranging from 0.7-2.6 g/L (0.07-0.26 g%) (49). Thereafter, 500 mL (10 subjects) or 750 mL (14 subjects) of blood were removed from a superficial vein over a time of 4-12 minutes. These volumes of blood correspond to 7% of body weight or 8-18% of the total blood volume. Despite the removal of these volumes of blood, the BAC curves followed the expected time course in the declining (postabsorptive) phase of ethanol metabolism. Two hours later, the blood previously removed was reinfused into the same test subjects. Although the ethanol content of this transfused blood was higher than the prevailing BAC, the rate of ethanol elimination was in the range 0.12-0.20 g/L/h (mean 0.15 g/L/h). The investigators reached the following conclusion (translated from German):

In summary, it is consequently established in our tests that a considerable blood loss of up to 18% of the blood volume and after a considerable infusion of blood substitute no variation in the course of the blood alcohol curve was observed in human subjects (49).

Several articles report the effects of hypovolemia on concentrations in blood of certain drugs other than alcohol. However, the experimental protocols mostly involve administration of test drug after the removal of an appreciable volume of blood (50, 51). An exception was a study of the disposition of codeine and its metabolite, morphine, in rats. The authors found small increases in concentrations of codeine and morphine in blood after removal of approximately 40% of the animal's blood volume (52). This was explained by movement of extracellular fluids, with higher concentrations of opiates, into the vascular system as a result of blood volume depletion.

Van Sassenbroeck et al. looked at the effect of hypovolemia (30% of blood volume) on the pharmacokinetics of gamma-hydroxybutyrate (GHB) in rats (53). This study is especially relevant because GHB and ethanol have similar pharmacokinetic properties, including distribution volumes (54). Both drugs mix completely with body water and there is no binding to plasma proteins and hepatic metabolism occurs by saturation kinetics (55). The hypovolemia had no significant effect on the concentration-time curves of GHB when the drug was administered intravenously after a known volume of blood was removed.

DISCUSSION

Overconsumption of alcohol and drunkenness are major problems for public health and victims of trauma and blood loss are often under the influence of alcohol when they are admitted to hospital for emergency treatment (56, 57). A person's BAC is important in a legal context because of the statutory alcohol limits that exist for driving a motor vehicle or engaging in certain safety-sensitive work (58). Care is needed whenever analytical results from hospital clinical laboratories are used in forensic investigations for rea-

sons discussed elsewhere (59). Forensic experts might be asked to interpret a person's BAC in relation to the amount of alcohol consumed, the degree of impairment or whether a driver was responsible for a traffic crash. Any life-saving medical treatment, such as administration of drugs, anesthetics, blood substitutes etc., needs careful documentation and consideration in any legal proceedings.

The impact of trauma and hemorrhagic shock on a preexisting BAC and rate of ethanol metabolism has been studied by forensic practitioners in Germany and the first article dates from 1937 (60). Results from experiments in animals, human volunteers and actual trauma victims undergoing life-saving emergency treatment are reviewed in the present article (46-49). By contrast, there is virtually no information available in English language journals about the impact of trauma and blood loss on a person's BAC, apart from an early study in mice (61).

The present review is well-motivated, considering the role played by heavy drinking and drunkenness in trauma injuries and road traffic crashes (8, 62). Furthermore, both victim and perpetrator in violent crimes are often under the influence of alcohol at the time (43). The person's BAC is compelling evidence when culpability for a road traffic crash is investigated or when criminal charges are brought for an assault. The effect of trauma, blood loss and administration of replacement fluids on a person's BAC and rate of ethanol metabolism often becomes contentious, especially when insurance claims are made and civil litigation occurs.

The conclusions from this literature survey are that neither trauma, massive blood loss nor replacement fluids have any significant effect on a preexisting BAC or the rate of ethanol elimination from blood. This stems, at least in part, from the physicochemical properties of ethanol, which is a drug that easily passes biological

Figure 2: Mean blood-alcohol curves in dogs ($n = 8$ animals) given an ethanol dose of 3.0 g/kg body weight by intravenous infusion and one hour later ~30-40% of blood volume was removed from an indwelling catheter resulting in hypovolemic shock. Graph modified and redrawn from reference (48).

membranes to distribute into TBW and does not bind to plasma proteins. There is no evidence that ethanol is sequestered in lipids or tissue depots, as occurs for many other drugs. However, blood samples taken after patients who suffer hypovolemic shock are likely to be more plasma-like in composition and contain a slightly higher concentration of ethanol (31).

Because resuscitating fluids rapidly equilibrate between intra- and extravascular fluids and TBW, the dilution effect on BAC is minimal. Kleemann et al. found that after giving large volumes of intravenous fluids to trauma patients, this treatment did not alter the rate of ethanol elimination from blood (46). However, each case should be considered individually and consideration given to the BAC and the pattern of drinking in relation to when the trauma occurred, the volume of blood loss, and the type and volume of replacement fluids.

The interpretation of BAC is more complicated in victims of burn trauma, owing to the resulting hypermetabolic state and accumulation of body water after burn injuries (63, 64). In trauma-related deaths, other factors deserve consideration, including decomposition and possible postmortem synthesis of ethanol from fermentation of glucose or other substrates (65). When government agencies and legislators introduced a statutory BAC for driving, they were considering blood samples taken under sterile conditions from living subjects and not blood from dead bodies taken during an autopsy (66).

CONCLUSION

In conclusion, this literature review indicates that trauma and massive blood loss exert insignificant effects on a person's BAC and rate of ethanol metabolism. However, if alcohol remains unabsorbed in the stomach when the trauma occurs, the reduced splanchnic circulation will tend to slow down and delay absorption of alcohol into portal venous blood. Much will depend on the quantity of ethanol unabsorbed in the stomach when the trauma occurs and the type of emergency treatment given. If trauma injuries or the life-saving surgical treatment interrupts hepatic blood flow, this will diminish the rate of ethanol metabolism.

The information contained in this review should be of interest to forensic practitioners called to testify about interpreting BAC in victims of trauma or to perform various forensic BAC calculations, such as back extrapolation, in pathological states such as hypovolemia and hemodilution.

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