The Clinical Significance of Variations in Ethanol Toxicokinetics

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ABSTRACT

Introduction: Many variables affect the interpretation of an isolated ethanol level in an acutely intoxicated patient. This review demonstrates the significant variability in metabolism and elimination of ethanol, how it can differ between individuals, and the clinical importance of these variables.

Discussion: Isolated ethanol values in a clinical scenario are only a snapshot of a dynamic process. The individual pharmacokinetic differences of people make it extremely difficult to estimate ethanol elimination rates or calculate previous ethanol concentrations at the time of an accident because of medical-legal reasons. Not only are the techniques used in measuring ethanol concentrations in bodily fluids (blood, serum, breath, and urine) not equivalent, but also the units used to report ethanol concentrations are often misinterpreted. Acute and chronic tolerance and social adaptive changes make interpreting this isolated ethanol level extremely difficult. The purpose of this review is to enable the clinician to appropriately interpret ethanol concentrations.

Conclusion: The clinical evaluation of a patient's inebriation is always more reliable than an isolated ethanol level for determining disposition. Only an estimation of a current serum ethanol level can be made if the blood draw was performed hours earlier. This review is clinically important because it shows the clinically significant variability in metabolism and elimination of ethanol and how it can differ between individuals. It will also describe different ways to measure ethanol concentrations and how to compare them. Finally, the interpretation of isolated ethanol levels will be discussed.

INTRODUCTION

Alcohol intoxication is a frequent diagnosis seen in the Emergency Department (ED) and may often be associated with other life-threatening illnesses that are masked by alterations in behavior or level of consciousness [1,2]. The intoxicated patient may present with sudden loss of consciousness, seizure, abdominal pain, chest pain, suspicion for the abuse of other drugs, or potential injuries following a motor vehicle accident. Often, these presentations may result in an extensive ED evaluation and possible hospital admission. This evaluation is more difficult in the intoxicated patient, and altered mental status from intoxication is made as a diagnosis of exclusion. However, interpreting these ethanol levels and correlating them with the clinical scenario can be complicated.

Many factors affect the interpretation of an isolated ethanol level in an acutely intoxicated patient. Although ethanol levels are measurable in serum, whole blood, expired air, urine, or saliva, these methods are not equivalent. The units used to report ethanol concentrations are not consistent. Depending upon a patient's acute or chronic tolerance, similar ethanol concentrations can cause a very different level of impairment. Most

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importantly, individual differences in social drinking habits and ability to metabolize ethanol can have remarkable differences on a patient's level of intoxication. Therefore, interpreting an isolated ethanol level in the ED is potentially misleading.

This review is clinically important because it shows the clinically significant variability in metabolism and elimination of ethanol and how it can differ from one individual to the next. It also describes different ways to measure ethanol concentrations and how to compare them. Finally, we will discuss the interpretation of isolated ethanol levels. Convenient tables and charts are included to aid in the processing of this information.

PHARMACOKINETICS OF ETHANOL

Understanding the dynamic process of ethanol absorption, metabolism, and elimination is the single most important factor in interpreting a static ethanol level. At the time of presentation, an initial ethanol level only provides a snapshot of a patient's intoxication. It neither indicates if the level is rising, falling, or at steady state, nor does it provide any information about the patient's ability to metabolize ethanol. It is imperative to remember that a dynamic process occurs around this isolated ethanol value.

Passive absorption of ethanol begins immediately upon ingestion and may continue during the ED evaluation if large quantities of ethanol were consumed shortly before presentation. Since approximately 20% of ethanol is absorbed through the stomach and the remaining 80% through the small intestine, gastric emptying is the most important factor contributing to the rate of rise and peak ethanol concentration [3].

Drinking ethanol after a meal not only decreases peak serum ethanol concentrations, but it also decreases total bioavailability [4]. This phenomenon is largely related to gastric emptying [5]. Aspirin and cigarette smoking slow the movement of gastric contents into the small intestine and have the same effect on ethanol absorption [4,6]. Even the amount of sugar in an ethanol-containing beverage can slow ethanol absorption by slowing gastric emptying [7]. Conversely, gastric bypass surgery, erythromycin, and ranitidine increase gastric emptying and thereby increase peak blood ethanol levels [8–10].

Several other variables further complicate an individual's ethanol absorption rate. For example, drinking ethanol on a full stomach will decrease its bioavailability. Even if an ethanol-containing beverage and a concurrently consumed meal are standardized, serum ethanol levels will vary more widely than when performing the same study on an empty stomach [4]. Additionally, first-pass metabolism by gastrointestinal and liver alcohol dehydrogenase (ADH) has a more profound effect on small ethanol doses than on large doses consumed during episodes of binge drinking [5].

Gender-related differences may contribute as well. Women have a greater ethanol bioavailability because they have less gastric ADH activity [11]. In addition to slight variations in volume of distribution, female gastric ADH activity is the reason women achieve greater blood ethanol levels, then men of similar weight, after consuming comparable amounts of ethanol.

We should note that the phases of the menstrual cycle are still a point of debate. While initial studies found differences in ethanol pharmacokinetics during different phases of the menstrual cycle, follow up studies failed to reproduce these effects [11,12,14,15]. Thus, it is difficult to consistently predict the effects on ethanol pharmacokinetics.

The volume of distribution (Vd) for ethanol most closely follows the distribution of total body water (usually 50–60% lean body weight for adults) [16]. Since women have less total body water per fraction of body weight, the same amount of ethanol consumed by a woman would reasonably result in a higher serum ethanol level than in a man of equal weight [17]. In addition, factors that alter peripheral circulation may affect the distribution of ethanol (18). Anything fostering peripheral vasoconstriction or impeding peripheral blood flow (such as cold ambient temperatures, peripheral vascular disease, and cardiac disease) may maintain elevated serum ethanol levels. Moreover, anything increasing peripheral blood flow (such as high ambient temperatures, muscular activity, and antihypertensive medications) will likely decrease serum ethanol levels. Since blood flow to the brain remains relatively constant, altering the blood ethanol concentration via any of these mechanisms may change the amount of ethanol delivered to the brain and change the level of intoxication accordingly.

The rate at which ethanol is eliminated also contributes to serum ethanol inter-individual variability. The vast majority (92–95%) of ethanol is metabolized by liver ADH [18]. Large polymorphisms in this enzyme's activity differ from race to race and from individual to individual [19]. The variability in ADH activity largely accounts for observed ethnic variations in ethanol elimination. 2–5% of ethanol is excreted unchanged in breath, urine, and sweat [18]. Ethanol clearance through these routes provides the opportunity for testing ethanol levels in breath or urine. At best, hepatic catalase provides a small amount of ethanol metabolism, but it is not clinically important. The remainder (<6%) of ethanol metabolism is via microsomal p450 enzymes [20]. 2E1 is the p450 subfamily most responsible for ethanol metabolism; however, 2A1 and 3A4 are also involved. These enzymes are inducible and are the reason higher ethanol metabolism rates are seen with chronic ethanol consumption [20]. Even though they account for a small percentage of ethanol metabolism, induction of p450 activity can increase ethanol elimination by more than 25%; this was shown in a baboon model [21]. Overall, the elimination of ethanol ranges from 10 mg/dL/hr to 25 mg/dL/hr (2.2 to 5.4 mmol/L/hr) [18]. A typical ED patient, as depicted by research performed by Brennan and colleagues, demonstrates a mean ethanol elimination rate of 19.6 mg/dL/hr (4.3 mmol/L/hr) [22]. However, documented literature shows many outliers and a wide range of ethanol elimination rates.

Drugs eliminated as a constant *percentage* per unit of time follow what is called first-order kinetics. On the other hand, drugs

Table 1: Theoretical peak serum ethanol level in mg/dL (mmol/L) calculated according to weight, gender, and number of drinks consumed. Chart assumes complete and immediate absorption.

		Men					
		Weight (Kg)					
		70	**80**	**90**	**100**	**110**	**120**
Number of Drinks	**1**	29 (6.3)	25.4 (5.5)	22.5 (4.9)	20.3 (4.4)	18.4 (4.0)	16.9 (3.7)
	2	58 (12.6)	50.7 (11.0)	45.1 (9.8)	40.6 (8.8)	36.9 (8.0)	33.8 (7.3)
	3	86.9 (18.9)	76.1 (16.5)	67.6 (14.7)	60.9 (13.2)	55.3 (12.0)	50.7 (11.0)
	4	115.9 (25.2)	101.4 (22.0)	90.2 (19.6)	81.1 (17.6)	73.7 (16.0)	67.6 (14.7)
	5	144.9 (31.5)	126.8 (27.5)	112.7 (24.5)	101.4 (22.0)	92.2 (20.0)	84.5 (18.3)
	6	173.9 (37.8)	152.1 (33.0)	135.2 (29.4)	121.7 (26.4)	110.6 (24.0)	101.4 (22.0)
		Women					
		Weight (Kg)					
		50	**60**	**70**	**80**	**90**	**100**
Number of Drinks	**1**	47.3 (10.3)	39.4 (8.6)	33.8 (7.3)	29.6 (6.4)	26.3 (5.7)	23.6 (5.1)
	2	94.7 (20.6)	78.9 (17.1)	67.6 (14.7)	59.2 (12.9)	52.6 (11.4)	47.3 (10.3)
	3	142.0 (30.8)	118.3 (25.7)	101.4 (22.0)	88.8 (19.3)	78.9 (17.1)	71.0 (15.4)
	4	189.3 (41.1)	157.8 (34.3)	135.2 (29.4)	118.3 (25.7)	105.2 (22.8)	94.7 (20.6)
	5	236.7 (51.4)	192.2 (41.7)	169.0 (36.7)	147.9 (32.1)	131.5 (28.5)	118.3 (25.7)
	6	284.0 (61.7)	236.7 (51.4)	202.9 (44.0)	177.5 (38.5)	157.8 (34.3)	142.0 (30.8)

A sample calculation used in creating this table is provided in Table 2. One drink is equal to a 12 oz beer (5% ethanol v/v), 1.5 oz of distilled liquor (40% v/v), or 5 oz wine glass (12% v/v).

metabolized as a constant *amount* per unit of time, like ethanol, follow what is called zero-order kinetics (Michaelis-Menton). Drugs following first-order elimination can be said to have a *half-life*. Ethanol is a drug that has no clear *half-life*. That is to say: at usual ethanol doses, the time it takes to reach half the serum ethanol concentration is completely dependent upon its original concentration. Ethanol's apparent half-life will decrease as serum ethanol levels fall. Thus, an apparently slow elimination rate may well be due to this zero-order phenomenon. All ED physicians have encountered patients with prolonged hospital stays because of extremely high ethanol levels. Even with the administration of copious amounts of intravenous fluids, a general ceiling for ethanol elimination is 25 mg/dL/hr (5.4 mmol/L/hr) [22].

In medical-legal cases, crude calculations are often used to estimate the maximum possible ethanol level achieved after consuming a reported number of beverages, or to calculate the ethanol level at the time an event occurred. In the ED, other calculations are performed to estimate the time required to decrease a patient's ethanol level to a tolerable range for discharge. Using these crude calculation methods, *Table 1* shows the theoretical peak serum ethanol concentrations as determined by the number of drinks consumed, weight, and gender. These calculations are purely theoretical and assume the beverages were immediately consumed and absorbed (as if administering the beverage via an intravenous line). In a more realistic manner, *Figure 1* shows serum ethanol concentrations with 95% confidence intervals after consuming one, two, or three drinks an hour for two hours. The beverages in this model are consumed in equal aliquots over the two hours and absorbed at a rate found in the literature [4–6, 18]. When known values and ranges for the absorption rate constant (k_a), volume of distribution (Vd), maximum elimination rate (Vmax), and the Michaelis-Menton constant (Km) are obtained from the literature, the peak serum ethanol levels and confidence intervals were generated using a Monte Carlo pharmacokinetic simulator (Boomer v 3.3.1) [16–22]. As opposed to the crude calculations in *Table 1*, *Figure 1* shows a more realistic potential range of ethanol concentrations over time. From this figure, a clinician can easily see the large error in estimating an ethanol level from using crude estimation tools.

The simulations in *Figure 1* demonstrate several limitations: (1) a single ethanol measurement in the ED does not demonstrate which side of the curve the patient falls, (2) many crude ethanol elimination calculations do not account for the large amount of variability found in the literature for each variable, (3) and not every variable can be simulated in the figure. This does not mean ethanol elimination calculations should not be performed, but rather, they should be done with ranges based on the available literature.

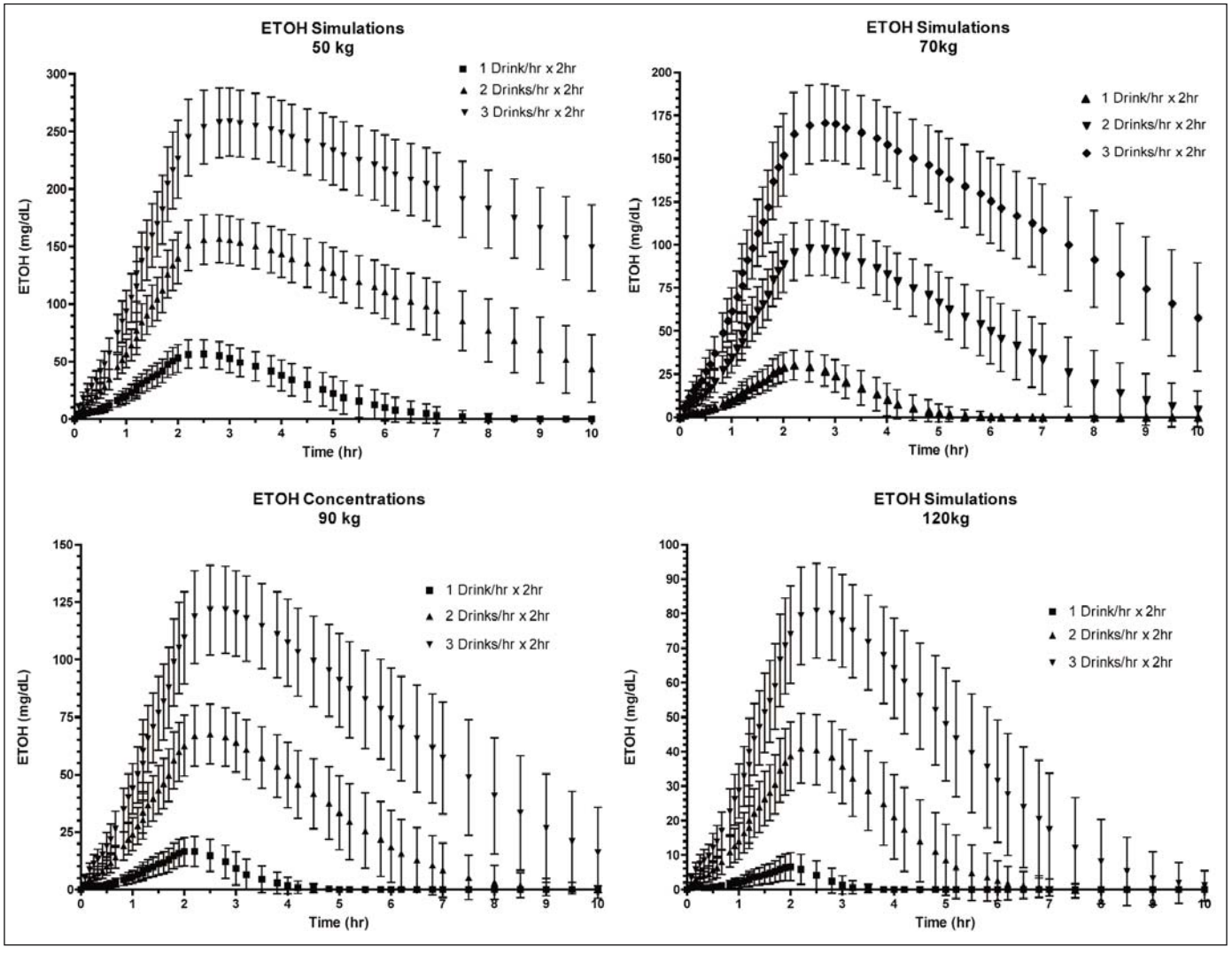

Figure 1: Simulations of serum ethanol concentrations over time for a 50, 70, 90 and, 120 kg adult after ingesting 1, 2, or 3 drinks per hour for 2 hours. Concentrations were generated with the Monte Carlo function of Boomer v 3.3.1 software using literature values and ranges for distribution volume, Vmax, and Km. One thousand simulations were performed with all three variables randomly modified per simulation. Isobars denote 95% confidence intervals. One drink is equal to a 12 oz beer (5% ethanol v/v), 1.5 oz of distilled liquor (40% v/v), or 5 oz wine glass (12% v/v).

UNITS USED IN REPORTING ETHANOL CONCENTRATIONS

A confusing array of units is used to report ethanol levels in body fluids: g/L, mg/L, mg/dL, g/dL, mmol/L, and % are some of the most commonly reported. The United States legal system uses a percent symbol (%) that is easily misinterpreted, but it is nothing more than g/dL. For example, a serum ethanol level of 0.8 g/L is equal to 800 mg/L, 80 mg/dL, 0.08 g/dL, 0.08%, or 17.4 mmol/L. A quick glance at these numbers easily explains the confusion that arises by misinterpreting an ethanol level by a factor of 10, 100, or even 1000. Misinterpreting a level higher than the actual value may remove concern in the evaluation of a comatose patient and prevent further work-up for other causes of altered mental status. On the other hand, misinterpreting a level in the other direction may result in the performance of unnecessary exams including a head CT, lumbar puncture, and innumerable other laboratory tests. Neither mistake would preclude liability from a missed diagnosis.

Inconsistent units are also used to report ethanol concentration in beverages, and it adds further confusion for the evaluating physician. Volume of ethanol per volume of beverage, expressed as a percent, is used on the packaging of manufacturers. This is normally reported as ethanol percent (v/v), or 5% (v/v) for a typical malt beverage, and it represents the *volume* of 100% ethanol per 100 mL (*volume*) of beverage. In other words, 5 mL of 100% ethanol in 100 mL of beer is a 5% (v/v) ethanol concentration. This is different than reporting the *weight* of ethanol per

Table 2: Sample serum ethanol concentration calculation as performed for Table 1

(1) 360 mL/can of beer × 5% ethanol (v/v) = 18 mL of 100% ethanol per beer
(2) 18 mL ethanol/beer × 0.8 gm ethanol/mL of 100% ethanol = 14.4 grams of ethanol/beer
(3) Vd of ethanol for 70 kg male = 0.7 L/kg × 70 kg = 49 L
(4) 14.4 grams ethanol / 49 L = 0.29 gm/L or 29 mg/dL or 6.30 mmol/L

29 mg/dL (6.30 mmol/L) would be peak theoretical serum ethanol concentration in a 70 kg man after one 12 oz beer. Variables estimated as follows: male Vd 0.7 L/kg, female Vd 0.6 L/kg, and ethanol specific gravity 0.8 gm/mL.

Table 3: List of key ethanol kinetics variables

Specific Gravity	0.789	
Volume of Distrubtion:[1]	**Male**	0.69 L/kg (range 0.63–0.76)
	Female	0.63 L/kg (range 0.54–0.71)
Serum [ETOH]: Blood [ETOH] [2]	1.16 (range 0.88–1.59:1)	
Rate of Elimination[3]	19.6 mg/dL/hr (range 10–25); 4.26 mmol/L/hr (range 2.17–5.43)	

[1] Reference 17; [2]Reference 23; [3]References 18, 21

total *volume* of solution which would be percent ethanol (*w/v*). This is confusing only because hospital laboratories report body fluids as *weight* of ethanol per *volume* of body fluid (i.e. milligrams of ethanol per deciliter of serum). Problems arise when calculating a projected serum ethanol concentration in milligrams per deciliter from a known volume of consumed ethanol. The volume of ethanol consumed must first be converted to milligrams by multiplying volume by the specific gravity of ethanol. Once the dose of ethanol (in milligrams) is known, one can calculate serum ethanol concentration by dividing dose by the Vd (see sample calculation in *Table 2* and ethanol kinetics variables in *Table 3*).

Proof, as a unit of measure, is a commonly used term among the lay public and, as such, requires mention as well. Simplified, proof is merely two times the percent ethanol (v/v) concentration. A study found that not only can the measured ethanol concentration of malt beverages vary from the reported label value, but also the intended ethanol concentrations can vary from 2.9 to 15.6% (v/v) [23]. Even though a "typical" malt beverage is assumed to have approximately 5% (v/v) ethanol, this study demonstrates ethanol concentrations may differ from what the public anticipates when consuming these beverages (*Table 4*).

MEASURING ETHANOL CONCENTRATIONS

Due to its distribution into total body water, ethanol concentration can be measured in almost any body fluid. Traditionally, ethanol has been measured in blood, serum, expired air, urine, and saliva. For convenience, law enforcement often uses expired air. When blood work is not needed, some EDs use urine to avoid unnecessary needle sticks. Serum is most frequently used in hospitals, yet whole blood is the legal standard. Unfortunately, no two body fluids are equivalent for determining ethanol concentrations.

Serum, Plasma, and Whole Blood Ethanol Concentrations

The gold standard for measuring ethanol concentrations is via blood or serum, and traditionally, a peripheral venous sample is obtained. Serum and plasma ethanol concentrations (albeit a subtle difference) have been shown to be equivalent, but whole blood concentrations are equivalent to neither serum nor plasma [24]. Because the water content of serum (or plasma) is higher than the water content of erythrocytes, the ethanol concentration in serum is usually higher than in whole blood [25]. On average, serum ethanol concentrations are 1.16 times higher than whole blood levels [24]. Rainey has shown that ethanol serum to whole blood ratio in ED patients can range from 0.88 to 1.59 [24]. This research demonstrates that a serum ethanol concentration can actually be higher, lower, or the same as a whole blood level. The large range partially results from the variability in individual serum, whole blood, and erythrocyte water content from one person to the next. Since most hospitals measure serum ethanol concentrations, problems arise when (for legal reasons) the whole blood ethanol concentration is estimated from serum using a fixed 1.16 ratio.

Additionally, the site of blood sampling can affect the result. Arterial and venous blood samples obtained at the same time can demonstrate considerable variability [26–27]. During the absorption phase, arterial levels exceed venous. For a short time at the completion of absorption, arterial and venous levels are equal, but in the post-absorptive phase, venous levels then exceed arterial. Thus, the venous to arterial ethanol concentration ratio can have remarkable variability and the exact ratio depends upon the pharmacokinetic phase and individual variability.

Despite these shortcomings, whole blood (or serum) ethanol concentrations are a precise means to evaluate ethanol concentrations [28]. Since venous whole blood or serum is the gold standard, all other means of measuring ethanol concentrations are compared to blood levels. As long as blood and serum ethanol concentrations are measured in a consistent manner (such as peripheral venous sampling) via a reliable method (such as gas chromatography), blood (or serum) is an effective method for determining ethanol concentrations [28–29]. Problems arise largely when whole blood ethanol concentrations must be converted from serum values for legal reasons.

Breath Ethanol Concentration

Breath ethanol concentration (BrEC) measurements are becoming more popular in the ED because of the non-invasive nature and the ability to obtain an immediate result. These are the same

Table 4: Measured ethanol concentrations as % v/v, mg/dL, and mmol/L in selected beer and malt beverages.

Brand	Measured Ethanol Concentration (%v/v)	Measured Ethanol Concentration (mg/dL)	Measured Ethanol Concentration (mmol/L)	Manufacturer
Amstel Light Beer	3.61	2.85	0.62	Amstel Brouwerij B.V.
Bass Pale Ale	5.38	4.24	0.92	Bass Brewers Ltd.
Beck's	5.22	4.12	0.89	Braueri Beck & Co.
Budweiser	4.76	3.76	0.82	Anheuser-Busch Brewing Co.
Budweiser Light	4.15	3.27	0.71	Anheuser-Busch Brewing Co.
Coors Banquet Beer	4.87	3.84	0.83	Coors Brewing Co.
Coors Light	4.11	3.24	0.7	Coors Brewing Co.
Corona Extra Beer	4.46	3.52	0.76	Cerveceria Modelo
Dos Equis XX Beer	4.34	3.42	0.74	Cerveceria Moctezuma
Foster's Lager	4.94	3.9	0.85	Carlton and United Breweries
Guiness EX Stout	6.08	4.8	1.04	St. James Gate Brewery
Harp Imported Lager Beer	5	3.95	0.86	Harp Brewing
Heineken Lager Beer	5.06	3.99	0.87	Heineken Brouwerijen
Labatt Blue	4.97	3.92	0.85	Labatt Breweries
Lowenbrau Dark Special Beer	4.68	3.69	0.8	Miller Brewing Co.
Michelob	5.25	4.14	0.9	Anheuser-Busch Brewing Co.
Michelob Light Beer	4.34	3.42	0.74	Anheuser-Busch Brewing Co.
Miller Genuine Draft Beer	4.62	3.65	0.79	Miller Brewing Co.
Miller Light	3.99	3.15	0.68	Miller Brewing Co.
Milwaukee's Best Beer	4.43	3.5	0.76	Miller Brewing Co.
Natural Ice Beer	5.6	4.42	0.96	Anheuser-Busch Brewing Co.
Newcastle Brown Ale	4.49	3.54	0.77	Newcastle Breweries Ltd.
O'Doul's Non-Alcoholic Brew	0.2	0.16	0.03	Anheuser-Busch Brewing Co.
Old Milwaukee	4.62	3.65	0.79	Stroh's Brewing Co.
Samuel Adams Boston Ale	4.56	3.6	0.78	Boston Beer Brewing Co.
Samuel Adams Winter Lager	6.77	5.34	1.16	Boston Beer Brewing Co.
Sapporo Black Stout Draft	5.44	4.29	0.93	Sapporo Beer
Sharp's Non-Alcoholic Brew	0.37	0.29	0.06	Miller Brewing Co.
St. Pauli Girl Beer	5.03	3.97	0.86	St. Pauli
Zima	4.97	3.92	0.85	Zima Beverage Co.

Adapted from J Anal Toxicol 2000; 24:202–210.

reasons law enforcement readily uses this method. Many different breath ethanol analyzers are manufactured and marketed for portability and durability.

Unfortunately, the convenience of estimating a blood ethanol concentration (BEC) from a breath sample is offset by the lack of accuracy in the measurement and the inability to retain a sample for confirmatory analysis later [30–31]. However, the precision (at least in cooperative adult volunteer studies) tends to be within the error expected from other hospital laboratory tests [32]. The largest contributors to error are both the ratio used to convert the BrEC to a BEC and the biologic variability in the breath sample provided by a patient [31].

Since a BrEC is merely an estimate of a BEC, a number or ratio is used to convert the BrEC to a BEC. The legal BEC:BrEC has been set at 2100:1. This simply means that the amount of ethanol in 2100 mL of exhaled air is the same amount in 1 mL of blood. This 2100:1 ratio has been repeatedly shown to be incorrect, but every breath analyzer purchased today uses the programmed ratio [30,32–35]. BrECs most closely resemble the amount of ethanol in the pulmonary arteries, rather than the gold standard of

systemic venous blood [27]. During absorption, ethanol concentration first rises in the portal circulation then sequentially in the right ventricle, pulmonary arteries, pulmonary veins, and systemic arterial circulation before distributing into tissues. Ethanol concentrations rise in venous blood last. After absorption is completed, systemic venous ethanol concentrations exceed arterial levels. Multiple studies have shown the 2100:1 ratio greatly overestimates BECs during the absorption phase which can last as long as 166 minutes [30–35]. Post absorption, the BrEC will slightly underestimate BEC. The only time the ratio approximates 2100:1 is at the time of peak venous blood ethanol concentrations [31]. At all other times, BrECs will poorly reflect the true venous BEC that is used as the legal standard. This may make little difference for treatment in the ED, but this may be important for the intoxicated individual still absorbing a stomach full of ethanol after getting behind the wheel. As noted, no perfect ratio exists throughout the course of pharmacokinetic phases.

The other large contribution to error from a BrEC is the biologic variability from the patient's breath sample [31]. For example, hyperventilating immediately before providing a breath sample can lower the reported BEC by 11%, and alternatively, breath holding can raise the level by 16% [36]. This occurs because BrECs are in equilibrium with bronchiolar tissue concentrations and not alveolar levels [30]. As the patient cools his bronchi by hyperventilating, less ethanol dissolves into the cooler air and will, in turn, decrease the measured value. If BrEC were in equilibrium with alveolar concentrations (like O_2 concentrations), then BrEC would not change with hyperventilation. Plus, unlike O_2 concentrations that plateau at end expiration, BrECs continue to rise with continued expiration because warmer air is continuing to volatilize more ethanol from the bronchioles throughout expiration. It is a myth that prolonged expiration, in order to sample alveolar air, is required for an accurate BrEC. Instead, it is the highest BrEC the patient can provide. Prematurely stopping exhalation during a breath ethanol test would greatly reduce the measured BrEC [30]. Theoretically, ambient air temperatures may alter BrECs too, but no study has researched this topic to date.

Saliva Ethanol Concentration

Saliva has demonstrated itself as a reliable means to measure ethanol and correlates well with blood ethanol levels [37–39]. A relatively new method of testing ethanol levels is via a saliva point-of-care test. OraSure Technologies Inc. (Bethlehem, PA) has developed a swab that collects saliva and, within 5 minutes, registers an ethanol concentration up to 350 mg/dL (76 mmol/L). Two studies have reported that OraSure's product has statistically significant correlation and is accurate with blood ethanol concentrations [37–38]. Even in the presence of oral blood, as with trauma patients, there was good correlation ($r = 0.976$; $p < 0.001$) (37). This test shows promise as a quick non-invasive way to measure ethanol levels for law enforcement or ED workers. However, the test does have its shortcomings. Some have reported that it can be difficult to obtain enough saliva, or the product fails to register an ethanol value even after presumably saturating the swab adequately [40]. In addition, no legal standard has been established for using saliva ethanol levels. In the future, this product may offer a convenient non-invasive alternative to using breath ethanol concentrations in the uncooperative patient without compromising accuracy.

Urine Ethanol Concentration

As we have explained with BrECs, measuring urine is merely a surrogate for blood levels. Even though several studies have shown urinary ethanol concentrations correlate with BECs, the values obtained do not accurately match blood levels and some arbitrary constant is sometimes multiplied by the urinary concentration to estimate the BEC [40–41]. Since urine is just plasma filtrate, urine ethanol levels should correlate with blood (or better yet, plasma) concentrations. However, urine can be stored in the bladder indefinitely. Initial urine ethanol concentrations will be diluted by urine formed prior to ethanol consumption, and urine remaining in the bladder long after BECs are zero may still have significant amounts of ethanol. The authors feel that testing urine ethanol levels is a good qualitative but a poor quantitative test.

TOLERANCE

Chronic Tolerance to ethanol is mainly the result of a combination of pharmacokinetic and pharmacodynamic changes. With chronic ethanol consumption, the pharmacokinetic change most responsible for tolerance is increased ability to metabolize ethanol. This occurs mainly by microsomal oxidase p450 2E1 [20]. Human and animal studies have shown that not only does the amount of smooth endoplasmic reticulum (the organelle responsible for microsomal oxidases) increase, but also that the activity of the enzyme 2E1 is specifically increased [42–44]. This effectively reduces peak levels and accelerates elimination rates [45]. The pharmacodynamic changes are secondary to neuroreceptor effects at serotonergic, stimulatory (such as NMDA), and inhibitory (such as GABA) receptors [46,47]. The changes that occur at neuroreceptors are complex and involve a blunted physiologic response from escalating ethanol doses. These changes also contribute to withdrawal syndromes if adequate ethanol levels are not maintained. Outside of pharmacokinetic and pharmacodynamic changes, research has demonstrated that social behavioral changes are learned during multiple drinking episodes. Over time, this translates into the appearance of diminished inebriation at similar ethanol concentrations [48]. In short, the changes that result from chronic tolerance can lead to the decreased appearance of inebriation after consuming large amounts of ethanol, and in turn it becomes increasingly difficult to interpret an isolated ethanol level in a patient with an unknown level of tolerance.

Acute Tolerance, a less known and less understood phenomenon, refers to a decreased level of inebriation when ethanol is consumed during a single drinking episode. The Mellanby effect is the term most often applied to acute tolerance, but the

Mellanby effect specifically refers to a decreased level of inebriation at the same BEC while levels are falling rather than rising. However, Mellanby's original research reported improved motor skills at constant BECs over time in a dog model [49].

Unfortunately, acute tolerance research is fraught with shortcomings. Original studies (including Mellanby's) used venous BECs [49–50]. A possible explanation for acute tolerance is a lag time between the rise and fall of venous BECs and brain tissue levels. We know that venous BECs rise more slowly than tissue levels during the absorption phase and fall more slowly in the elimination phase. This lag time would cause venous BECs to underestimate brain levels during absorption and overestimate levels during elimination. This gives a false sense of an effect because venous BECs are not an exact representation of tissue levels. However, additional studies using BrECs confirm the Mellanby effect in humans [51–52]. This is important because we know that brain and arterial ethanol concentrations are highly correlative and BrECs are a closer measurement of arterial levels [27]. Another problem with acute tolerance literature is the poor effort to correct for learning. During the course of an experiment, a subject will naturally improve at a motor task the more times the task is performed. Falling ethanol concentrations occur late in the experiment, giving the subject ample opportunity to practice the skill used as the primary outcome measure. So the Mellanby effect may merely be a result of learning the motor skill over the course of experimentation. At least one study, however, was reportedly able to correct for learning and still confirm the Mellanby effect [51]. Lastly, acute tolerance during steady-state ethanol concentrations has been hard to reproduce in humans. Two studies using BrECs at steady-state fail to demonstrate an acute tolerance effect [53–54].

Despite inconsistent or poor evidence, most agree acute tolerance truly exists. Many other human and animal studies have reported the existence of the effect [50–52,55]. In addition, the peak level of inebriation appears to precede the peak BEC, and so evidence favors the effect [56]. Assuming acute tolerance exists, patients may have the subjective sensation that their level of inebriation is decreasing despite a rising BEC. Therefore, acute tolerance may explain why the actual measured BEC does not reflect what is happening at the tissue level, namely brain tissue.

CONCLUSION

This review has several limitations. The basis for interpreting ethanol levels is only made available by the latest literature review. The literature often complicates matters by providing marked variability in results that are mainly due to differences in ethanol sampling techniques and non-standardized patient populations. Furthermore, our attempt to simplify ethanol pharmacokinetics via our simulations are subject to modeling bias and cannot account for every variable responsible for ethanol absorption, distribution, metabolism, and elimination (*Figure 1*).

This paper attempts to show the difficulty in clinically interpreting ethanol levels on an individual basis. The less experienced drinker and the experienced alcoholic's single ethanol level may clinically differ at presentation. A multitude of factors contribute to the error and interpretation of an isolated level. All these factors should be kept in mind when evaluating not only the intoxicated patient, but also the intoxicated patient with a medical or traumatic disease. Unfortunately, the evaluating physician cannot possibly know how an isolated ethanol level contributes to an individual patient's neurological examination. As part of our inpatient medical toxicology service, the authors have admitted teenage girls, who are awake and alert, with ethanol levels greater than 300 mg/dL (65 mmol/L). So it is clear that the interpretation of these ethanol levels must be evaluated on a case-by-case basis. No exact correlation exists between an ethanol level and a patient's mental status. Generally, the circumstances leading to the ED evaluation will often shed light on possible medical or traumatic conditions. When the circumstances are unknown, it is always better to err on the side of more aggressive evaluations and interventions. No standardized method for treating the intoxicated patient can be easily done.

Premature discharge of inebriated patients has resulted in extended liability for physicians when patients cause harm to themselves or others [57]. When other medical conditions are ruled out and the intoxicated patient is competent with a normal neurological exam, the patient is often ready for discharge. For determining disposition, the clinical evaluation of the patient's state of inebriation is always more reliable than an isolated ethanol [57]. As is shown in *Figure 1*, it is difficult to make an accurate estimation of a serum ethanol level from a blood draw performed hours earlier. However, a potential range of serum ethanol levels can be provided. Always use caution in evaluations and discharges of inebriated patients.

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