Introduction

In emergency medicine, the most common legal drug encountered worldwide is ethanol (alcohol). Alcohol is consumed by a large portion of people in most countries. The harmful and hazardous consequences of acute alcohol intoxication are an international problem and a significant contributing factor to injuries and death. About 20% of emergency department admissions involve alcohol [1], and overall, alcohol is a direct or indirect cause of approximately half of all intentional and unintentional injuries resulting in death [1,2]. Non-quantitative clinical tools to assess intoxication may include casual observation (e.g., odor of alcoholic beverage, behavioral disturbances), which may lead to screening, brief interventions, referral, and treatment (SBIRT). In some instances, a method to make quantitative estimates of intoxication based upon pre-admission patient history may be useful and often of clinical and medicolegal value. For example, estimating the blood alcohol concentration (BAC) in overdose patients based on reported alcohol intake may be required to assist in a diagnosis or medication treatment plan before a chemical test is available or in estimating when a patient will be sober enough to ethically be released from the ED. This is particularly important because clinical signs of intoxication are not reliably observed at lower BACs [3-5], even though impairment and risk for further injury may be significant [6]. In hospitals, chemical testing using clinical (e.g., ADH method) or other methods (e.g., breath testing, gas chromatography), while objective, only provide an objective result at the time the sample is obtained. In medico-legal matters, accurate estimates of intoxication at different points of time are also useful as is a simple method to convert serum alcohol to whole blood alcohol (often the legal standard in alcohol matters is the concentration of alcohol in blood, not serum). Finally, clinical alcohol researchers and others, including medical epidemiologists, report on the consequences of intoxication but their conclusions are limited to the relationship between a pre-admission event (injury) and treatment record (including blood alcohol results) obtained hours later. During that time, the BAC may be higher or lower due to changes in absorption and elimination. Estimating intoxication at the time of an injury, rather than at the time of the blood test would provide a more accurate insight into the relationship between intoxication and injuries.

Medical records often include self-report or witness-provided data regarding drinking history. An admission of drinking or signs of intoxication may precipitate a blood test to quantify the concentration of alcohol in blood. Alternatively, when reliable information regarding total alcohol intake is provided with other patient information, alcohol intoxication can be estimated mathematically. Methods for such estimates have been published to assist legislators in their deliberations regarding drinking-driving laws [7], for use by epidemiologists, researchers [8-11], and forensic scientists in defining what constitutes “a drink” [11-15], but are subject to the limitations described.

Methodology

How to Calculate Whole Blood Alcohol from Serum or Plasma Alcohol: Many hospitals, particularly in the US, measure alcohol in serum, not whole blood. The matrix used is important in interpreting such results because alcohol is distributed throughout the watery portions of the body,
including the blood. Since many clinical laboratories use serum as the matrix to analyze alcohol and serum contains more water than the whole blood from which it is derived, the concentration of alcohol in whole blood is less than that of the serum in proportion to their respective water contents.

Early studies reported the serum: whole blood alcohol ratio to be about 1.1 to 1.2 [16], with an accepted average of 1.18 [17,18]. A hospital serum alcohol can be reasonably and quickly converted to a whole blood equivalent by dividing the serum concentration by 1.18 or multiplying the serum value by the reciprocal (e.g., serum x .85). When compared with whole blood test results in the same subject, we have found this conversion accurate when physiology is relatively normal. The potential limitation of this method is that it does not account for medical conditions of hemodilution or hemoconcentration that might follow medical intervention or medical conditions. For example, aggressive fluid replenishment will dilute alcohol in blood resulting in a lower than actual BAC, as may conditions such as anemia or severe blood loss. To correct for this, the hematocrit may be used to mathematically calculate the blood water content. That value, when divided by water content of serum, provides a conversion factor for that patient [19]. Because women have a lower average hematocrit than men [19], different conversions may apply. We find that paired serum and blood test results are within about ± 5 milligrams using this method and we are currently working to refine this further.

Equations 1 a,b,c. Calculating whole blood alcohol equivalents from serum alcohol.

a. BAC conversion for men = (((Hct x 0.645) + ((100–Hct) x 0.95)))/ 95
b. BAC conversion for women = (((Hct x 0.608) + ((100–Hct) x 0.95)))/ 95
c. or simply: (serum alcohol concentration) x (0.85)

How to Calculate BAC for Clinical Estimates: Once a whole blood alcohol equivalent is calculated (Equation 1), and additional basic information is obtained, a quick estimate of the BAC for clinical purposes is possible based on a reliable pre-admission drinking history, if available. This method, which is an updated and algebraic variation of Widmark’s original work in 1932 requires the patient’s body water weight, the number of drinks, and number of hours since the first drink and assumptions about the rate of elimination (see 11).

Equation 2. Rapid BAC estimate for clinical purposes.

\[ \text{BAC} = \frac{g/Vd \times Bl_{\text{H2O}} - \beta \times (t_s + t_p)}{1} \]

Where:

\[ g = \text{number of drinks} \times 14 \] (a standard is defined as a 12-ounce beer of 5% v/v alcohol or 1.5 oz. of 80 proof liquor, each of which contain 14 grams of absolute alcohol).

\[ Vd = \text{volume of distribution (}.58 \text{ for men, .47 for women)} \]

For example, if a 160 pound (73 kg) male patient consumed 10 drinks in the three hours before injury and is examined one hour afterwards, the estimated BAC would be \( \left( \frac{140}{73 \times .58} \right) \times (80.65) - (15 \times 4) \), which computes to about 207 mg/dL or .21% at the time of examination. This formula provides a quick clinical estimate of intoxication and can be done on a hand calculator or smart phone. More accurate estimates can be obtained using more specific anthropometrics and a range of absorption and elimination rates discussed later in this review.

Correlating Intoxication with a Pre-Admission Event: An estimate of intoxication based on self-report is useful for a snapshot of intoxication, it does not provide insight about intoxication prior to hospitalization (e.g., at the time of injury) or later (at time of discharge). Although much is known about the relative risk for a fatal injury at a particular BAC, such estimates are useful in epidemiological research relating intoxication and risk for non-fatal injury. Various mathematical models have been published that can predict BACs at different points in time if sufficient information if available [4,7,20-22]. These models require information about the drinking period, assumptions about the rates of absorption and elimination, anthropometric characteristics of the subject, specific drink input data and scientific or other assumptions. A discussion of the strengths and weaknesses of such approaches is discussed elsewhere [11].

Historically, models using single rates of absorption and elimination and variability associated with an assumed Vd for all subjects have been criticized [23]. We now describe a more specific and accurate method for estimating the BAC. This is essentially a two-compartment model based on a series of mathematical algorithms to account for individual anthropometrics (age, weight, height and gender) and different rates of absorption and a range of elimination rates likely to account for the overwhelming majority of subjects. This model is then compared with BACs from published studies. The algorithm accounts for different compartments, drink input, gastric absorption, distribution in body water and elimination, the components of which are described below.

Body Compartments: Body compartments can include: gastrointestinal, portal, hepatic, tissue and blood compartments. For our purposes, gastrointestinal alcohol and alcohol in blood are treated as separate compartments. Hepatic and portal/tissue/blood compartments are accounted for in the distribution and elimination of alcohol discussed later. The two initial compartments in this model are As and Ab, where:

\[ \text{As} = \text{alcohol in the stomach/small intestines} \]
\[ \text{Ab} = \text{alcohol in the blood} \]

Drink input: The drink input constant, \(K_1\), in grams of alcohol ingested per hour based on subjective data or calculated from an objective chemical test by algebraically rearranging Equation 2 to calculate grams of alcohol consumed. This is discussed in detail elsewhere [11].

\[
K_1 = \left(0.79 \text{ grams of alcohol per mL} \times 29.57 \text{ mL/fluid ounce} \right) \times \left(\text{percent alcohol/100} \times \text{fluid ounces per drink} \times \text{number of drinks} \right) / \text{total drinking time in hours}
\]

Absorption of alcohol: Under experimental conditions, a small quantity of alcohol is absorbed through the walls of the stomach but under normal (social) drinking conditions, the overwhelming majority of alcohol enters the circulation through the small intestine. The rate of gastric emptying is a function of many factors, including force and frequency of peristalsis and determined largely by gastric volume. Gastric emptying is proportional to the distension of the stomach, which is directly related to the volume within the stomach and the presence or absence of food. While the rate of emptying may increase with larger volumes, the time to empty is predictably longer because of the larger volume [24]. In practice, small amounts of alcohol reach maximum concentrations rapidly whereas larger amounts require more time and are, to some degree, subject to other factors. The time to maximum BAC does not usually correspond with the time required for total absorption.

The drink constant is \(K_1\) (into the stomach) and the absorption constant (from the stomach into the blood) is \(K_2\).

\[
K_1 = \text{drink input constant (grams consumed per hour)}
\]

\[
K_2 = \text{absorption constant} = \left(60/100 \times r(\text{abs})\right)
\]

Where \(r(\text{abs})\) is a percent of \(A_s\) per minute and corresponds to grams of alcohol absorbed per gram \(A_s\) per hour. The \(r(\text{abs})\) or \(K_a\) (in some literature), is approximately .01 to .06/min [25], which corresponds to a percent of the total alcohol available in the stomach (\(A_s\)).

With drinking, the increase of \(A_s\), which is \(d(A_s)/dt\) in calculus terms, is shown in the following equation. Each of these terms is in units of alcohol grams per hour:

Equation 3. \(d(A_s)/dt = K_1 - K_2 (A_s)\)

This is a first-order differential equation for \(A_s\). It is linear as far as the alcohol in the stomach is concerned (movement through and out of the intestines is rapid and considered one compartment). Assuming there is no alcohol in the stomach when drinking starts, the solution to this equation is shown in Equation 4.

\[
\text{Equation 4. } A_s = (K_1/K_2)(1-\exp(-K_2 t))
\]

Where \(\exp(-K_2 t)\) means “\(e\) to the power of (minus \(K_2\) times \(t\)), and \(t\) is time in hours.

Equation 5. Portion of absorbed alcohol in grams is \(K_2(A_s)\):

\[
(K_2/K_1)(1-\exp(-K_2 t)) = K_1(1-\exp(-K_2 t))
\]

Because in the first minutes of drinking \(K_2(A_s)\) is very low and metabolism begins almost immediately, mathematically a pre-load dose (14 grams of alcohol) in ten minutes is used to avoid a net sum of zero alcohol entering the blood after passing through the liver.

This is the input to the blood compartment (and the start of non-linearity). The output from the blood compartment is a function of distribution and primarily hepatic metabolism.

Distribution: Alcohol from the first compartment (gastrointestinal system) enters the second compartment where it is distributed in the blood and throughout total body water. The volume of distribution (\(V_d\)) is a function of the ability of the drug to bind to plasma protein, tissue, etc. Alcohol is very hydrophilic, does not bind to plasma proteins and easily distributes throughout the watery compartments of the body. Isotope dilution [26], and other studies of the total body water [27], allow estimates of the total water based on age, weight and gender and avoid the limitations of Widmark’s generic rho factor [28]. We use the term \(V_d\) here to refer to the total volume (liters) of water in which alcohol can be distributed based on individual characteristics and the work of Watson [27], who described total body water in the following subject pools.

Equation 6. Estimating \(V_d\) for men less than 16 years old:

\[
V_d = -21.993 + \left(0.406 \times (\text{pounds}/2.2045)\right) + \left(0.209 \times \text{height in inches}/2.54\right)
\]

Equation 7. Estimating \(V_d\) for men 17–86 years old:

\[
V_d = 2.447 - \left(0.09516 \times \text{age}\right) + \left(0.1074 \times \text{height in inches} \times 2.54\right) + \left(0.3362 \times (\text{pounds}/2.2045)\right)
\]

Equation 8. Estimating \(V_d\) for women less than 16 years old:

\[
V_d = -10.313 + \left(0.252 \times (\text{pounds}/2.2045)\right) + \left(0.154 \times \text{height in inches} \times 2.54\right)
\]

Equation 9. Estimating \(V_d\) for women 17–84 years old:

\[
V_d = -2.097 + \left(0.1069 \times \text{height in inches} \times 2.54\right) + \left(0.2466 \times (\text{pounds}/2.2045)\right)
\]

Accounting for Alcohol Elimination: Alcohol elimination (mg/dL/h) varies between and sometimes within individual subjects [29]. Rather than use a single average rate of elimination, a range of \(r(\text{elim})\) is recommended. Elimination is a linear function of \(t\) and where \(\beta_{\text{elim}}\) is the selected range of rates (e.g., 10 mg/dL/h, 15 mg/dL/h or 20 mg/dL/h). Since the pioneering work of Widmark (1932), and for many decades, it was believed that alcohol metabolism followed zero-order kinetics [28]. Evidence now suggests that at very low BACs (usually less than 30 mg/dL), Michaelis–Menten first order kinetics apply [22]. Calculations based on measured BACs of less than 30 mg/dL must account for dynamic changes in metabolism at low BACs or avoided. Since BAC estimates below 30 mg/dL are rarely of clinical value, first order kinetics is not included in this model.
Differences in first pass metabolism by gastric alcohol dehydrogenase (GADH) may or may not occur [30–33], as may gender-related differences in hepatic metabolism [34,35]. Such effects along with body water composition may contribute to the observed pharmacokinetic differences between some men and some women. Even so, GADH has a minor role in first pass metabolism and the overwhelming majority of alcohol is metabolized in the liver and eliminated. The actual rate of elimination is rarely known but centrally weighted at 15 mg/dL/h [23,28], the use of a wide range of elimination rates (β) is recommended to account for individual differences. In our research, we use elimination rates of .01%, .015% and .02%/hr, although higher rates have been reported in some clinical populations [36,37].

Equation 10. Alcohol elimination:

\[(β_{1-n}) \times (\Sigma t)\]

where \(β_{1-n}\) is the range of elimination rates selected (e.g., 10 to 20 mg/dL/h) and \(\Sigma t\) is the time in hours from the start of the blood draw, for example.

Previously, in Equation 4, the amount of alcohol entering the blood was expressed as: \(A_b = (K_1(1 – \exp(-K_2t))\). When the variables of alcohol input, absorption, distribution and elimination are considered together, the BAC over time can be calculated from Equation 12.

Equation 11. The BAC over time:

\[(K_1(1 – \exp(-K_2t)) – (\beta_{1-n})/(t)/(.08065/\Sigma Vd))\]

To test the validity of this approach, an alcohol literature search was conducted for publications with sufficient subject and dosing details, and plotted or tabularized blood alcohol data over time collected in the course of various human studies. The results predicted from the model (Equation 12) were compared with blood alcohol concentration estimates from six representative subjects from five studies: Figure 1 [37], Figure 2 [38], Figure 3 [20], Figure 4 [39], Figure 5 [37] and Figure 6 [40]. The absorption rate variable is based on a percentage of As that resulted in peak blood alcohol concentrations about of 30 to 90 minutes. This rate is adjustable (e.g., from .02 to .06%/min) to correspond to the peak BACs and time of the known BAC, and elimination rates of 10, 15 or 20 mg/dL/hr were applied in each case. The time or drinking period varied from 10 minutes for lowest BAC study [39], to 240 minutes for the highest BAC study [40]. Subjects were tested after an overnight fast with a light meal or snack prior to drinking. One study [37], compared subjects with a “full stomach” with “empty stomach” subjects. In another study [20] a lower last dose was administered at 90 minutes. This variable range of drinking conditions was deemed to be representative of the range of actual drinking conditions against which to compare the model.

Results

Figures 1–6 show actual BAC data (solid squares) derived from the studies selected superimposed on the predicted BAC estimates (A, B and C). For all figures, Analysis A is based on a high r(abs) with a peak BAC of approximately 30 minutes post drinking and a high r(elim), Analysis C is based on a low r(abs) with a peak BAC at approximately 90 minutes and low r(elim) and Analysis B is based on a widely observed average r(abs) of 45 minutes and average r(elim) of 15 mg/dL/hr. Results are presented as g% in the figures. Combining r(abs) with r(elim) as described yields maximum and minimum BACs. The effect
of even higher or lower rates of absorption and elimination can be calculated or interpolated from the analysis as performed.

It can be seen that even though the test conditions and alcohol doses varied among studies and subjects, all predicted BACs (A–C) corresponded extremely well with the actual data. These results demonstrate the importance of using a range of assumptions in such analyses and the accuracy of this methodology. Since most drinking occurred with very little or no food in the stomach, the actual BAC data were best predicted by analyses A and B and less by analysis C. Data points outside the predicted range produced by A through C were within 5 mg/dL (less than .005%) of the projections and infrequent.

**Discussion**

The results from this study demonstrate that accurate estimates of alcohol intoxication can be made based on available anthropometric data, a range of known pharmacokinetic parameters, a reliable drinking history and objective chemical test results. In clinical practice, estimates of intoxication based on drinking history should not supersede objective testing. Nevertheless, the usefulness of this study is three-fold. First, applying such methodology will be particularly helpful to epidemiologists who study the relative risk for injury associated with a BAC at about the time of injury. Currently, most relative studies correlate injury with the BAC at the time of death and therefore, do not address the issue of relative risk for more frequent non-fatal injuries. Second, allowing emergency medicine physicians to make estimates of intoxication at the time of examination before chemical test results are available may be useful in better diagnosing signs or administering medications. Finally, in forensic medicine, an understanding and appreciation of these methods will be useful when queried about the interpretation of alcohol results in a legal matter where the lab reports a serum value but the legal standard is whole blood alcohol, or where estimating the BAC at the time of an event is of legal interest.

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**References**


