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Best-practices approach to determination of blood alcohol concentration (BAC) at specific time points: Combination of ante-mortem alcohol pharmacokinetic modeling and post-mortem alcohol generation and transport considerations

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ABSTRACT

Alcohol concentrations in biological matrices offer information regarding an individual's intoxication level at a given time. In forensic cases, the alcohol concentration in the blood (BAC) at the time of death is sometimes used interchangeably with the BAC measured post-mortem, without consideration for alcohol concentration changes in the body after death. However, post-mortem factors must be taken into account for accurate forensic determination of BAC prior to death to avoid incorrect conclusions. The main objective of this work was to describe best practices for relating ante-mortem and post-mortem alcohol concentrations, using a combination of modeling, empirical data and other qualitative considerations. The Widmark modeling approach is a best practices method for superimposing multiple alcohol doses ingested at various times with alcohol elimination rate adjustments based on individual body factors. We combined the selected ante-mortem model with a suggestion for an approach used to roughly estimate changes in BAC post-mortem, and then analyzed the available data on post-mortem alcohol production in human bodies and potential markers for alcohol production through decomposition and putrefaction. Hypothetical cases provide best practice approaches as an example for determining alcohol concentration in biological matrices ante-mortem, as well as potential issues encountered with quantitative post-mortem approaches. This study provides information for standardizing BAC determination in forensic toxicology, while minimizing real world case uncertainties.

1. Introduction

Alcohol (e.g., ethanol or ethyl alcohol), one of the most commonly consumed psychoactive drugs in the world, is often used to promote social interaction, is generally accepted and legal in many countries. However, alcohol is a depressant that can impair a person's ability to operate a motor vehicle; determining blood alcohol concentration (BAC) is therefore one of the most prevalent forensic chemical analyses performed for criminal and medical purposes (Robinson and Harris, 2011). For example, a recent review article evaluating 69 epidemiological studies found that 52% of driving-related fatalities and 35% of driving-related injuries were associated with positive alcohol tests (Schalast et al., 2011).

Although alcohol metabolism has been studied for over 100 years, accurately predicting BAC following alcohol consumption remains an active scientific research area (Nicloux, 1899; Hamill, 1910). Precise estimation of the BAC at a given time point is complicated by individual variability in body and metabolism characteristics (e.g., age, body mass index, liver health, state of nourishment, state of hydration and basal metabolic rate), variability in mass or concentration of alcohol present in beverages (e.g., beer, wine, spirits), and the biological matrices sampled to determine the BAC.

Determining BAC is particularly challenging when an impaired driver is fatally injured in an accident. In such instances, the BAC

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measured in a blood sample collected from the driver post-mortem is used to determine the level of the driver's impairment. However, various factors can affect post-mortem BAC measurements that do not typically affect ante-mortem measurements: alcohol metabolism phase, presence of a preservative in the collected sample, sample storage condition, variation in sampling media, putrefaction, and post-mortem alcohol neoformation. These factors are particularly important in accident situations in which the body is not recovered and promptly refrigerated. A direct post-mortem BAC measurement may not accurately characterize a driver's impairment level at the time of death. In many instances, the BAC measured after an accident is much higher than the level predicted by simple reconstruction of the driver's recent alcohol and food consumption (Wigmore, 2011).

The purpose of this paper is to present a best-practices ante-mortem alcohol modeling approach combined with a simple post-mortem alcohol concentration analysis to generate accurate BAC predictions before and after the time of death, thereby optimizing and standardizing forensic approaches in real world cases. The objectives of this study were to: 1) evaluate the relationships between alcohol concentrations in various biological matrices; 2) generate an empirical modeling approach for correlating post-mortem alcohol concentrations with pharmacokinetic (PK) modeled ante-mortem concentrations up until the time of death; 3) describe factors associated with determining whether alcohol concentrations measured post-mortem are due to ante-mortem ingestion of alcohol or post-mortem synthesis of alcohol by microorganisms; and 4) describe best practices for determining ante- and post-mortem alcohol concentrations with a focus on potential sources of error.

2. Background

2.1. Human metabolism of alcohol

Alcohol (CH_3CH_2OH) is a small, polar molecule that accumulates in water-rich areas of the body, and does not significantly diffuse into fatty tissues. Following ingestion, alcohol is absorbed slowly in the stomach and rapidly in the small intestines. The rate of alcohol absorption is affected by the rate of gastric emptying, which in turn is influenced by various factors such as food ingestion (Holt, 1981; Holt et al., 1980; Sedman et al., 1976; Lin et al., 1976).

Various enzymes are responsible for alcohol metabolism including alcohol dehydrogenase (ADH) in the liver, and aldehyde dehydrogenase (ALDH) and CYP2E1 in the brain and liver (Fig. 1) (Matsumoto and Fukui, 2002; Israel et al., 2013). Approximately 90–98% of ingested alcohol is metabolized through the alcohol dehydrogenase + aldehyde dehydrogenase pathway and other phase II metabolic pathways, while the remaining 2–10% is excreted un-modified in breath, sweat and urine (Jones, 2010). In cases of low exposure, alcohol is metabolized and eliminated without significant physiological effects. The body's first-pass metabolism can prevent small doses of alcohol from reaching systemic circulation (Jones, 2010). However, once a threshold exposure is reached (which varies among individuals), the metabolic enzymes are saturated, and excess alcohol begins to accumulate in the bloodstream. Alcohol in the blood will diffuse across the blood brain barrier, causing inebriation and impairment of physiological responses. Alcohol's progressive physiological effects follow a dose-response relationship with respect to physiological effects in drinkers who do not suffer from alcoholism (Table 1) (Chong, 2014; Dubowski, 2006).

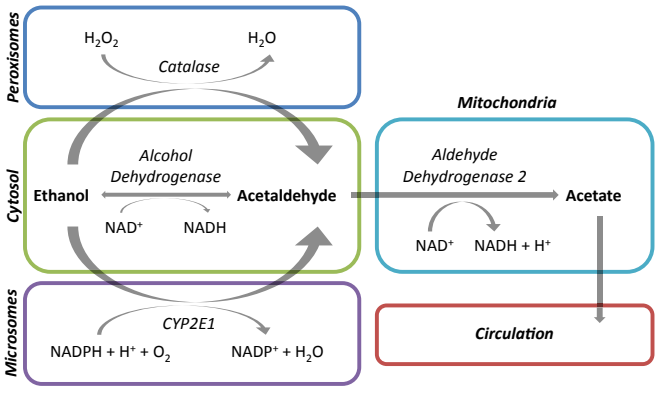

Fig. 1. Metabolic pathway for elimination of alcohol in humans.

Alcohol concentration in the body changes as a function of time. BAC generally increases following an exponential curve to a maximum after initial alcohol ingestion as it is absorbed by the body, then decreases linearly as it is eliminated until very low levels (<0.01–0.02%) of BAC, at which point the decrease becomes exponential (Jones, 2010). The increasing BAC phase is generally called the "absorption phase", while the decreasing phase is called the "elimination phase". The mass of alcohol ingested is important in determining BAC, and the alcohol content varies widely by type of drink. Additionally, the percentage of alcohol by volume (ABV) impacts the rate of absorption; drinks with 10–30% ABV are absorbed the fastest; stronger or weaker drinks are absorbed more slowly (Kelly and Mozayani, 2012). Also, during the absorption phase, equilibrium is not reached, and the blood alcohol concentration may not fully reflect an individual's intoxication state (Wigmore, 2011). In the elimination phase, equilibrium is reached, and BAC is on the decline, thereby better reflecting the biological influence of alcohol (Wigmore, 2011).

2.2. Ante-mortem alcohol pharmacokinetic modeling approaches

Widmark presented an empirically-based formula in 1932 that considered the exponential metabolic absorption rate constant, the zero-order elimination rate for alcohol, and the Widmark Factor (WF), an empirical rate constant accounting for the body's water content and volume alcohol distribution into body compartments as described below (inverse first-order dependence) (Posey and Mozayani, 2007).

$$BAC = \frac{A_{ingested}\left(1 - e^{-kt}\right)}{rW} - (\beta t)$$

where,

BAC = Blood alcohol concentration (g/L)
t = Time since ingestion of alcohol (h)
$A_{ingested}$ = Mass of alcohol contained in the drink (g)
r = Widmark Factor (unitless)
W = Body weight (kg)
k = Absorption rate constant (h^{-1})
β = Elimination rate ((g/L)/h)

The Widmark Equation remains the "gold standard" approach for retrospectively estimating BAC (Posey and Mozayani, 2007; Widmark, 1932). Further developments in BAC estimation in recent years included Derr's 1993 development of compartmental physiologically-based pharmacokinetic (PBPK) models for four different ethnicities, and Umulis et al., 2005 addition of reversible enzyme kinetics (Derr, 1993; Umulis et al., 2005). PBPK models can