Regulatory Toxicology and Pharmacology 94 (2018) 163–171

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Providing context for phosphatidylethanol as a biomarker of alcohol consumption with a pharmacokinetic model

Ted W. Simon

Ted Simon, LLC, 4184 Johnston Road, Winston, GA, 30187, USA

ARTICLE INFO

Keywords:
Alcohol consumption
Blood alcohol concentration
Phosphatidylethanol
PEth 16:0/18:1
Pharmacokinetics

ABSTRACT

Phosphatidylethanol (PEth) is increasingly used as a biomarker of heavy drinking. Many different forms of PEth can form in red blood cell membranes from the action of the enzyme phospholipase D. PEth has a very long duration in blood because, in contrast to other tissues, RBCs lack the enzymes that degrade PEth. Because this biomarker is relatively new, interpretations of the analytical measurements of PEth may be misinterpreted and the resulting predictions of actual alcohol consumption inaccurate. Hence, a simple pharmacokinetic model of PEth was developed to provide a means of contextualizing these analytical results. A number of alcohol consumption scenarios and current clinical screening levels were examined with the model.

1. Introduction

Phosphatidylethanol (PEth) is increasingly being recognized as a potential biomarker of chronic alcohol consumption for forensic use (Isaksson et al., 2011). A number of homologues of phosphatidylethanol are formed in the membranes of erythrocytes when alcohol is present. The reaction between ethanol and phosphatidylcholine is catalyzed by phospholipase D (PLD). This enzyme is ubiquitous in mammals; for many years, the function of this enzyme remained unknown; recent knowledge indicates PLD and its normal product, phosphatidic acid, play a role in signaling pathways related to inflammation, cancer pathogenesis and neurodegenerative disorders. Phosphatidyl alcohols have varied effects on downstream targets but physiological changes due to altered PLD signaling appear relatively insignificant (Brown et al., 2017).

A large number of distinct homologues of PEth form in blood exposed to alcohol. The two most abundant are PEth 16:0/18:1 and PEth 16:0/18:2. The homologue generally analyzed by testing laboratories in the US is PEth 16:0/18:1 (Gnann et al., 2010).

Estimates of the half-life of PEth 16:0/18:1 and other homologues range from 1 to 13 days and the half-life varies greatly between individuals (Javors et al., 2016). A recent meta-analysis demonstrates good clinical efficiency of PEth for detecting chronic heavy drinking (Viel et al., 2012). The variability in the pharmacokinetics of PEth, however, restricts the ability of this biomarker to predict alcohol consumption with any certainty. The choice of a cut-off value is complicated by the lack of any quantitative pharmacokinetics to date (Dasgupta, 2015).

PEth was first used as a marker of alcohol consumption in the late 1990s; the analytical method was high-performance liquid chromatography with evaporative light scattering detection (HPLC-ELSD); this method could not separate PEth homologues and had a detection limit of almost 600 ng/ml (Hansson et al., 1997; Gunnarsson et al., 1998; Gnann et al., 2009; Varga et al., 1998). In 2009, a method was introduced with a much lower detection limit utilizing LC-ESI-MS/MS following miniaturized organic solvent extraction and reversed phase chromatography (Gnann et al., 2009, 2010). Schröck et al. (2014) provide a useful description of analytical methods and a table of detection and quantitation limits for the various methods.

Differing choices of PEth homologues as alcohol biomarkers as well as the change in analytical methodology with a tenfold lowering of detection limits has created uncertainty regarding the interpretation of PEth results. Weinmann et al. (2016) note: “According to an agreement between Swedish laboratories, the limits of decision for excessive alcohol consumption has been defined at ≥ 0.3 μmol/l” or 215 ng/ml and these authors refer to the original work in Swedish (Helander and Hansson, 2013). A number of other cutoffs representing varying degrees of potentially excessive alcohol consumption have been suggested. Recent cutoff values are summarized in Table 1 and the range of these cutoffs reflects the varying comparison endpoints, i.e. abstinence vs. moderate drinking vs. drunk driving. The recent interest in developing new cutoffs likely stems from advances in PEth analysis and the comparative advantages of this biomarker (Winkler et al., 2013).

Here, an empirically-derived pharmacokinetic model for PEth 16:0/18:1 pharmacokinetics is developed and then used to provide context and credible ranges for PEth analytical results corresponding to varying

E-mail address: ted@tedsimon-toxicology.com.

https://doi.org/10.1016/j.yrtph.2018.01.029
Received 26 November 2017; Received in revised form 29 December 2017; Accepted 30 January 2018

Table 1
Suggested cut-points for PEth 16:0/18:1. Abbreviations: DUI: driving under the influence; DBS: dried blood spot; AUDIT: Alcohol Use Disorder Identification Test; ROCC: receiver-operator characteristic curve; Sn: sensitivity; Sp: specificity.

Cut-point value	Population	Sample method	Statistical methods	Source
≥700 ng/ml	Blood samples from 142 Swiss drivers stopped for DUI; BAC separated as BAC > 0.016 g% or < 0.016 g%	Whole blood	ROCC: Sn = 0.659, Sp = 0.684	Schröck et al., 2016
≥400 ng/ml for severe misuse	Mixed population from medical ICUs, alcohol detoxification units and healthy volunteers (AUDIT)	DBS	ROCC: Sn = 0.778, Sp = 0.931	Afshar et al., 2017
≥250 ng/ml any alcohol misuse;	Mixed population from medical ICUs, alcohol detoxification units and healthy volunteers (AUDIT)	DBS	ROCC: Sn = 0.873, Sp = 0.879	
≥221 ng/ml for chronic and excessive consumption	Inpatients in an alcohol detoxification unit (n = 50) and control non-alcoholic volunteers (n = 18)	Whole blood and DBS	ROCC: Sn = 0.86, Sp = 1.0	Kummer et al., 2016
≥80 for 4 drinks/d	222 patients with chronic liver disease self-reporting alcohol use with ethylglucuronide in urine and hair also tested	Whole blood	ROCC: Sn = 0.91, Sp = 0.77	Stewart et al., 2014
≥6.3 ng/ml indicating any drinking	46 healthy Danish volunteers randomized to either abstinence or 1.3 drinks/d for women and 2.7 drinks/d for men for 3 months	DBS	ROCC: Sn = 0.84, Sp = 0.83	Kechagias et al., 2015

Table 2
Model Parameters. Abbreviations: BMI: body mass index; BW: body weight.

Parameter	Distribution	Parameters	Dependencies	Source
Anthropometric parameters				
Gender	Binomial	1, 0.5	NA	NA
Body weight (M)	Lognormal	μ = 4.4626 σ = 0.2112	BMI: ρ = 0.86	Portier et al. (2007); Revicki and Israel (1986)
Body weight (F)	Lognormal	μ = 4.2979 σ = 0.2502	BMI: ρ = 0.86	
BMI (M)	Lognormal	μ = 3.3620 σ = 0.1889	BW: ρ = 0.86	McDowell et al. (2008)
BMI (F)	Lognormal	μ = 3.3312 σ = 0.2381	BW: ρ = 0.86	
Height (m)	Calculated as sqrt(BW/BMI)			
Widmark Model parameters				
Widmark factor r (M)	Normal	M = avg. of methods; CV = 9.2%	BMI: ρ = 0.6748	Posey and Mozayani (2007); Maudens et al. (2014); Gullberg (2007)
Widmark factor r (F)	Normal	M = avg. of methods; CV = 9.2%	BMI: ρ = 0.7755	
Absorption rate constant	Johnson SB	γ = 1.5 δ = 0.61 ε = 0.5 λ = 29.5	Varies with food intake (not modeled)	Fig. 2 of Uemura et al. (2005); Flynn (2004, 2006)
Elimination (M)	Johnson SB	γ = 1.28 δ = 1.44 ε = 0.01 λ = 0.03	None	Fit to data in Table 1 of Pavlic et al. (2006); Flynn (2004, 2006)
Elimination (F)	Johnson SB	γ = 0.552 δ = 1.121 ε = 0.01 λ = 0.03	None	
PEth model parameters				
Bmax	Lognormal	μ = 0.4600 σ = 0.2086	Kd: ρ = 0.7342	Developed here from Gnann et al. (2012), Javors et al. (2016) and Schröck et al. (2017)
Kd	Lognormal	μ = −4.640 σ = 0.5103	Bmax: ρ = 0.7342	
Elimination	Lognormal	μ = −5.80 σ = 0.4856	None	

daily consumption of alcohol. The Widmark model for blood alcohol concentrations (BAC) has proved useful in both legal and clinical settings for many years. The simple model presented here serves to characterize a long-term biomarker of alcohol consumption. The inter-individual variability in PEth results adds difficulty to the interpretation of cutoffs; however, a reduction in PEth concentration over time suggests an individual is reducing consumption or is abstinent. Hence, a recommendation is made to obtain at least two samples with at least one week between them, consistent with a recent clinical study (McDonell et al., 2017).

2. Theory/Calculation

Modeling was performed in MS-Excel using Monte Carlo simulation with the Yasai add-in (http://www.yasai.rutgers.edu/). The time step for modeling was 0.25 h or 15 min and time-dependent parameters were expressed on an hourly basis. Model parameters are provided in Table 2 and described below. Dependencies in the model were achieved