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Phosphatidylethanol in Blood as a Marker of Alcohol Dependence

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Keywords

Phosphatidylethanol; reference values; alcohol-related disorders

Abstract

Aim: To establish the cut-off value of phosphatidylethanol (PEth) concentration in the blood for detecting alcohol dependence. **Materials and Methods:** Using the method of high-performance liquid chromatography - tandem mass spectrometry (HPLC - MS), the concentration of PEth in the blood of 127 alcohol-dependent men undergoing hospital treatment was determined. To assess the diagnostic accuracy and to establish the cut-off values of PEth concentration, a ROC (receiver operating characteristic) analysis was performed. Statistical data processing was carried out using the Statistica 10.0 program. **Results:** At a cut-off PEth concentration of 495 ng/ml, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 99 %, 96 %, 98 %, 98 % respectively. **Conclusion:** The results of the study indicate the high diagnostic reliability of PEth as a biochemical marker of alcohol dependence.

Introduction

Alcohol abuse is a leading risk factor for global disease and death burden [1]. In many countries, the number of people suffering from alcohol dependence is growing [1]. As a rule, such patients are admitted to the clinic at the late stages of the disease, which significantly reduces the chances of recovery [2]. Therefore, methods to facilitate prompt identification of alcohol abuse would be helpful. The use of biochemical markers is considered an objective alternative to self-reports of alcohol consumption, the disadvantage of which is low validity due to recall bias or deliberate falsification [3].

Biomarkers aiming to detect excessive alcohol consumption have been used in clinical routine for many years, but none of the traditional indirect biological markers are sensitive and specific enough for the diagnosis of alcohol abuse [4]. During the past decade, the advances in the identification and application of direct alcohol biomarkers have been made [5]. In addition to having a high sensitivity and specificity, one of its advantages is the ability to distinguish between moderate and heavy alcohol consumption [6].

Phosphatidylethanol (PEth) seems to be one of a few promising direct biomarkers of alcohol abuse and has been widely used over the latest years due to its long detection window compared with other direct alcohol biomarkers [7]. PEth is an abnormal phospholipid, which is formed extrahepatically by the action of phospholipase D on phosphatidylcholine in the presence of ethanol [8].

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The PEth homologue 16:0/18:1 has a half-life of 4 to 10 days and can be detected in blood up to 4 weeks after alcohol has been eliminated from the body [9].

Available research evidence indicates significant variability of the reference cut-off of PEth concentration for discrimination between different levels of alcohol consumption [5]. It was proposed to use a PEth concentration of 20 - 200 ng/ml (0.03 - 0.30 μmol/L) as a cut-off for "significant" alcohol consumption, and a concentration > 200 ng/mL as a cutoff for "heavy" alcohol consumption [8]. Another study recommended using a PEth cut-off of 221 ng/L for chronic alcohol abuse [9]. The lack of consensus on the reference cut-off concentration for different patterns of alcohol consumption complicates the use of PEth as a biochemical marker of alcohol dependence.

The aim of this study was to establish the cut-off value of PEth concentration in the blood for detecting alcohol dependence.

Materials and methods

The study involved 127 alcohol-dependent men undergoing inpatient treatment at the Grodno regional clinical center "Psychiatry-Narcology". The control group consisted of 136 moderately drinking (no more than one standard drink per day) representatives of the general population. The study was approved by the clinic's Ethics Committee, and written informed consent was obtained from all participants. Venous blood was samples upon patient admission, prior to the initiation of any medical or detoxification procedures. Whole blood samples collected in Vacutainer were kept at room temperature in sampling room and during transport. The concentration of PEth (homologue 16:0/18:1) in the blood was determined by high-performance liquid chromatography - tandem mass spectrometry (HPLC - MS) [10]. Statistical data analysis (descriptive statistics, correlation analysis, dispersion analysis, logistic regression) was performed using Statistica, version 10.0 (StatSoft Inc., Tulsa, OK, USA). The Shapiro-Wilk criterion was used to test statistical hypotheses about the type of distribution. Differences between independent groups were analyzed using one-way ANOVA followed by assessment using the Shapiro-Wilk test. ROC (receiver operating characteristic) analysis was performed to assess diagnostic accuracy (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)), as well as to determine the optimal threshold concentration of PEth. To assess the prognostic value, the area under the ROC curve (AUC) was determined. The diagnostic accuracy of the marker increases as this indicator approaches unity. The 95 % confidence interval of the AUC was calculated according to DeLong. The Youden index was used to determine the threshold level.

Results

The median value of the PEth concentration in the blood of alcohol-dependent men was significantly higher than in the blood of moderate drinkers: 2058 (CI: 1433 – 2830) vs. 31.8 (CI: 23.2 – 86.8) ng/ml; $p<0.0001$. Binary logistic regression analysis was conducted to model the relationship between PEth concentration (ng/ml) and group status (0 = control, 1 = alcohol dependence). The resulting model was of the form:

$$\text{logit}(P) = \beta_0 + \beta_1 \times \text{PEth},$$

where P is the probability of belonging to the alcohol-dependent group, β_0 is the intercept, and β_0 is the regression coefficient for PEth concentration. (Table 1).

Receiver Operating Characteristic (ROC) analysis identified a cut-off value of 495 ng/ml for PEth concentration in the blood, above which the likelihood of alcohol dependence was high. At this cut-off value, the model demonstrated strong performance with sensitivity of 99 %, specificity of 96 %, PPV of 98 %, and NPV of 98 %. The area under the ROC curve (AUC) was 0.99, indicating a very good predictive value of the model.

Discussion

The results of present study should be interpreted in the context of existing literature. According to the results of previous studies, the content of PEth in the blood of alcohol-dependent patients varies widely: 0.23 - 16.5 μmol/l (153 - 11583 ng/ml) [8,9,11,12]. In a study

Table 1. Results of binary logistic regression estimating the probability of alcohol dependence based on PEth concentration in the blood.

Term	Coefficient (β)	Standard Error	Z-value	P-value
Constant	-4.81	1.18	-4.08	0.000
PEth	0.008	0.002	4.02	0.000

involving 57 alcohol-dependent patients undergoing detoxification, the concentration of PEth varied within 0.63 - 26.95 μmol/l (median – 4.97 μmol/l) [8]. In one study involving 78 inpatients and 66 outpatients with alcohol dependence, the average concentration of PEth in inpatients and outpatients was 7.7 ± 3.2 μmol/l and 3.4 ± 2.6 μmol/l, respectively. The median value of PEth concentration in inpatients and outpatients was 7.5 (1.9 – 15.9) μmol/l and 2.9 (0 – 13.1) μmol/l, respectively [9]. In another study, which included 36 alcohol-dependent patients undergoing outpatient treatment, the PEth concentration at the time of admission varied within 0.05 – 1.2 μmol/l (median – 0.23 μmol/l) [11]. Significant variability in the concentration of PEth in the blood of alcohol-dependent patients may be due to the lack of a standard protocol for determining this indicator.

Previous studies have shown the high diagnostic reliability of PEth [8,9,12]. According to Wurst et al., the sensitivity of PEth was 100 % [8]. Hartmann et al. found that at a cut-off values of 0.36 μmol/L, the sensitivity and specificity of PEth in diagnosing alcohol dependence was 94.5 % and 100 %, respectively [12]. According to Aradottir et al., the sensitivity of PEth was 99 % (98 % and 100 % for inpatients and outpatients, respectively) [9].

The findings from present study confirm the high detection capability of PEth as a biomarker for chronic excessive drinking. As for the cut-off concentration of PEth calculated in this study, it turned out to be significantly higher compared to the cut-off values proposed by other authors. The reason for this discrepancy may be the lack of clear inclusion criteria in the experimental group in many studies, which are often formulated as "significant" or "heavy" alcohol consumption [6].

In conclusion, the results of this inpatient treatment study highlighted the clinical value of alcohol biomarkers as objective measures of chronic alcohol abuse. These findings demonstrate a good clinical efficiency of PEth for detecting alcohol dependence. Although PEth 16:0/18:1 seems very promising as a biomarker for alcohol dependence, further research is necessary focusing on the determination of cut-off value and identification of confounding factors.

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Conflict of Interest

None to declare.

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