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Measurement of Ethanol Use in a Chronic Pain Population Using the Biomarker Phosphatidylethanol

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Abstract

Background: Measurement of ethanol (EtOH) use in chronic pain patients has always been a challenge. Current biomarkers are easily confounded, giving unreliable results. Self-reporting is unreliable. Phosphatidylethanol (PEth) is a recent EtOH biomarker that shows promise as an alternative measure of EtOH. **Methods:** Twenty patients were included in this study. All were 21 years of age or older and had chronic pain for greater than 3 months. Patients took the Alcohol Use Disorders Identification Test (AUDIT) questionnaire. Blood was collected for PEth testing. Correlation between Audit score (0 - 40) and PEth level (ng/mL) was done with the Pearson Product-moment correlation coefficient (SPSS). Values are means ± S.E.M. Significance at $p \leq 0.05$. Opioid use with EtOH use was also examined. **Results:** Twenty patients were enrolled, 17 (85%) males and 3 (15%) females. AUDIT scores were 8.1 ± 1.4. PEth levels were 178.3 ± 43.5. Eighty-five percent of patients had Audit scores indicating mild to moderate use of EtOH while 15% had severe use. PEth levels indicated 70% mild to moderate EtOH use and 30% heavy use. The correlation coefficient between the Audit score and PEth was 0.219 ($p = 0.353$) and not significant. Twenty-five percent of patients in the study were on opioids. The average PEth level in these patients was 273 ± 101.7. **Conclusions:** There is a poor correlation between self-reporting of EtOH use per AUDIT and PEth levels. Twenty-five percent of patients in the study were also on opioids, with PEth levels indicating high levels of EtOH consumption in this group. This suggests that self-reporting of EtOH use is inadequate in the chronic pain setting to detect actual EtOH use.

Keywords

Chronic Pain, Alcohol, Phosphatidylethanol, PEth, EtOH

1. Introduction

EtOH use has proven to be a significant risk factor contributing to overdose deaths for patients on opioid medications [1]. It is widely recommended that patients on opioid medications avoid the use of EtOH while under the influence of opioids. This recommendation is typically codified in the form of an opioid agreement or contract that is endorsed by the patient prior to initiation of opioid treatment. There is also a myriad of other medications used to treat chronic pain that can pose a safety risk to patients, most notably benzodiazepines, when combined with opioids [2].

Currently, there is no typical or widely accepted test used routinely to detect EtOH use in chronic pain patients. Phosphatidylethanol (PEth) is a lipid byproduct formed from ethanol as a reaction involving phosphatidylcholine and catalyzed by phospholipase D (PLD) in red blood cells [3]. PEth has been shown to detect consumption of EtOH in the clinical setting for several weeks [4].

PEth is becoming more widely used in the medical field as an accepted measure of EtOH use. The availability of PEth testing has reduced eligibility for liver transplant candidates with alcohol related liver disease [5]. The use of PEth is also being more widely used within the specialty of addiction medicine to monitor abstinence and EtOH use levels [6] [7]. PEth testing has also been utilized for security purposes and in the workplace [4].

In the chronic pain population, regular use of EtOH as a pain management strategy has been postulated to be as high as 25% - 28% [8]. This is higher than believed to be the case in the general population. While EtOH can act as an analgesic, it can also complicate treatment of chronic pain and clearly has adverse effects on health, particularly when used heavily [9]. Many of the medications that are prescribed for chronic pain interact in a deleterious way with EtOH. Opioids and EtOH in combination have been shown to increase rates of respiratory depression and increase the chances of death [10]. Several other medications frequently employed in the treatment of chronic pain also interact poorly with EtOH. Even over-the-counter medications for pain such as aspirin, non-steroidal anti-inflammatory drugs, and acetaminophen can interact with EtOH in a potentially fatal way.

Self-report is currently the most common method for determining the use of EtOH in chronic pain clinics. There are several tools or surveys available to determine its use. The Alcohol Use Disorders Identification Test (AUDIT) survey is one survey developed for this purpose. It has been tested for reliability and validity extensively [11]. The AUDIT survey is widely used in alcohol research (12). Despite this, self-report of EtOH use has been shown to be an unreliable predictor of its use. This is particularly true for patients who are considered problem drinkers [12].

A need for a reliable and easy-to-interpret measure of EtOH use not confounded by organ dysfunction, with a longer half-life than blood alcohol content, and not dependent on self-reporting is needed to identify patients with recent EtOH use or misuse in the outpatient chronic pain population.

This study has used the AUDIT questionnaire as a self-report of EtOH use. PEth levels were then measured, and the degree of correlation was evaluated between the AUDIT questionnaire and PEth levels in chronic pain patients. Examination of concurrent opioid use in this population was also evaluated as a secondary end point.

2. Methods

This is a single center prospective study. IRB approval was obtained in 5/2020 and the study was closed to enrollment in 4/2024. The study was approved by the appropriate Institutional Review Board (IRB), and written informed consent was obtained from all subjects, a legal surrogate, or the requirement for written informed consent was waived by the IRB.

Requirements for inclusion in the study included age 21 years or older, pain for greater than 3 months, and self-reported 2 or more alcoholic beverages per day, at least five days a week. Exclusion criteria included patients who had less than 3 months of pain, patients who were under 21 years of age and women who were pregnant or lactating. Twenty patients were enrolled in this study.

The schedules of the clinicians involved in the study were screened one to two weeks ahead of time. The social history of patients was evaluated. If alcohol use was present in the social history then patients received a phone call prior to their upcoming appointment. During the phone call with the patient a brief description of the study occurred, and the patient was asked if they drank 2 or more alcoholic drinks per day at least 5 days a week. If the patients answered this question affirmatively, they were asked if it was acceptable to them to further discuss the study when they came for their clinic visit.

During the clinic visit, patients met with a research team member and discussed the study. If the patient remained interested in participating in the study, a formal consent process occurred and the patient signed the consent for participation in the study.

After the consent was signed the patients were given the AUDIT questionnaire to complete via self-administration. Blood was then collected on sample cards after a finger stick which was supplied by the U.S. Drug Testing Laboratory (USDTL). Patient information was de-identified and samples were sent to USDTL for analysis. (USTDL, 1700 S. Mount Prospect Road, Des Plaines, IL 60018).

Specimens were analyzed using a previously published method [13]. PETH was detected in standard dried blood spot punches (3.1 mm) using an AB Sciex 6500 liquid chromatography-tandem mass spectrometry (LC-MS/MS) system.

We have used the cutoff of 20 ng/mL as a reference point [4]. Below 20 ng/mL alcohol consumption is considered absent or light. Above 20ng/mL alcohol consumption is considered moderate, up to 200 ng/mL. Above 200 ng/mL EtOH use is considered heavy. If patients had PEth concentrations > 200 ng/mL they were contacted via telephone and counseling services were offered.

The AUDIT test score ranges from 0 - 40 corresponding clinically to various

levels of EtOH use/misuse. Cutoff values are sex specific. AUDIT mild to moderate EtOH use female ≥ 5 and male ≥ 8. AUDIT severe EtOH use female > 13 and male > 16 [14]. Data were analyzed using SPSS. Values are means ± S.E.M. with significance at $p \leq 0.05$.

3. Results

Patient demographics are presented in Table 1.

Table 1. Patient demographics.

Characteristics		Patients (n = 20)
Age		63 (46 - 97)
	Sex (male)	17
	Sex (female)	3
Race		
	White	15
	Black	3
	Hispanic	2

Table 2 shows a comparison of EtOH use as evaluated by the AUDIT questionnaire and PEth blood values. The mean AUDIT score was 8.6 ± 1.4 with a PEth (ng/mL) value of 178.8 ± 43.5. Eighty-five percent of patients had AUDIT scores indicative of mild to moderate use of EtOH while 15% had severe use. This contrasted with PEth levels that indicated 70% mild to moderate EtOH use and 30% heavy use.

Table 2. Comparison alcohol use audit questionnaire with Peth blood values.

Alcohol Information	Patients (n = 20)
Audit score (0 - 40)	8.1 ± 1.4
PEth (ng/mL)	178.8 ± 43.5
Mild to Mod use (Audit)	17 (85%)
Severe Use (Audit)	3 (15%)
Mild to Mod Use (PEth)	14 (70%) 71.6 ± 14.6
Heavy Use (Peth)	6 (30%) 428.7 ± 67.9
Values are mean ± S.E.M.	
Audit Mild to Mod Use Female ≥ 5 Male ≥ 8	
Audit Severe Use Female ≥ 13 Male ≥ 16	
Peth Mild to Mod Use 20 - 200 ng/mL	
Peth Heavy Use > 200 ng/mL	

The correlation (Pearson's r; SPSS) between Audit score (0 - 40) and PEth (ng/mL) is shown in Figure 1. The correlation coefficient (r) was 0.219 ($p = 0.353$).

The result is not significant.

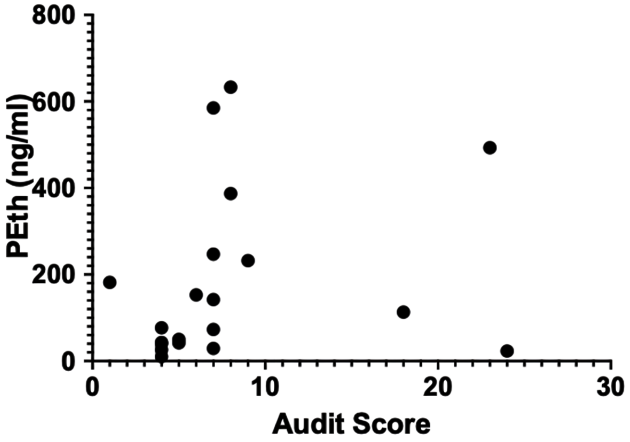

Figure 1. Correlation between audit and PEth in chronic pain patients.

Table 3 shows the relationship between concurrent alcohol and opioid use. Patients prescribed opioids and using EtOH were 25% (5/20) of the group. The PEth level in patients on opioids and using alcohol was 273 ± 101.7 ng/mL.

Table 3. Alcohol and opioid use in patients.

Patients	Characteristic
Patients EtOH and Opioid	5/20 (25%)
PEth (ng/mL) in EtOH and Opioid Patients	273 ± 101.7
All patients male. N = 5	
Heavy EtOH use > 200 ng/mL	
Values are means ± S.E.M.	

4. Discussion

This study examined the use of the AUDIT self-reporting questionnaire and the PEth biomarker for EtOH use in chronic pain patients. It has long been suspected that self-reporting of EtOH use is an inadequate measure of EtOH consumption. This study indicates that this is likely also the case for chronic pain patients in the outpatient clinic setting.

The correlation coefficient between the Audit score and PEth values was 0.219 and was not significant ($p < 0.05$). The chronic pain patients involved in the study underrepresented the extent to which they used EtOH with 17 (85%) indicating mild to moderate use of EtOH by AUDIT scores and 3 (15%) indicating heavy use. When the PEth data was analyzed 14 (70%) patients were shown to use EtOH at a mild to moderate level, while 6 (30%) were using EtOH at a heavy level. Out of the group that was involved in heavy use of EtOH by measurement of the PEth levels, the average PEth level was 428.7 ± 67.9, significantly above the 200 ng/mL cutoff for the definition of heavy use. This indicates that there are certain patients

who are using significantly more EtOH than they indicate on the AUDIT questionnaire.

This data is particularly concerning in light of the fact that these patients were aware that they were going to be tested for EtOH use with the PEth study after completion of the AUDIT questionnaire. You would expect this foreknowledge to skew the data on the AUDIT questionnaire toward being more in line with the data determined with the PEth levels. Possible reasons for this discrepancy could include fear of judgment by the health care team, not keeping track of how much EtOH is consumed, and fear of consequences. Those consequences could include being taken off opioid medications. In the opioid agreement that is signed prior to the initiation of opioids in clinic, consumption of EtOH is not allowed while on opioid medications.

Of the patients involved in the study, 5/20 (25%) were on opioids, and all of these patients were male. The average PEth level in these patients was 273 ± 101.7. With the cutoff for heavy use for EtOH by PEth being 200 ng/mL, these results suggest that many of the patients on opioids are consuming large amounts of EtOH. This is a safety risk for the patients involved, and an unexpected finding of a secondary measure of the study.

The use of urine drug screens in patients on pain medications has become ubiquitous over the last several decades, and highly recommended. Urine drug screens in the chronic pain setting are used for several reasons including: to verify compliance with treatment, to decrease rates of diversion and to verify the absence of illicit substances in the urine. This last point, the verification of the absence of illicit substances in the patient's urine, is important from a patient safety perspective. Chances of overdose death dramatically increase when a patient on opioid medications combines the appropriately prescribed opioids with illicit substances [15].

EtOH, like illicit substances, can also have negative effects on patient safety in pain clinics. The implementation of PEth as an objective measure of EtOH use in chronic pain patients has the potential to markedly increase safety for these patients. Opioid medications used with EtOH are a clear risk that can be addressed. Other medications that are used to treat chronic pain that can also increase morbidity and mortality in the setting of EtOH use include: muscle relaxants, antineuropathics, acetaminophen, and non-steroidal anti-inflammatory medications [2].

EtOH use is not accurately characterized by many of the currently available tests in chronic pain patients. Blood alcohol content (BAC) can identify patients who are acutely intoxicated, though BAC levels drop rapidly once alcohol ingestion is terminated [16]. Other biomarkers, such as Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Carbohydrate Deficient Transferrin (CDT) γ-Glutamyltransferase (GGT), and Mean Corpuscular Volume (MCV), can be confounded by age, gender, liver pathology, BMI and nonalcohol-related illnesses, among other things [17]. The accurate interpretation of these lab results can also be complex and time-consuming, making routine use in clinical practice cumbersome.

Ethyl glucuronide (EtG) and fatty acid esters (FAEE) can be detected in the hair of patients. This can be useful for long-term alcohol use, though less useful in the short to intermediate term. EtG and FAEE can also be affected by hair treatment including coloring, bleaching or straightening, and samples cannot be obtained in patients with short hair [18]. The urine tests ethyl glucuronide (EtG) and ethyl sulfate (EtS) have also recently been used in the clinical setting to detect EtOH. PEth has been shown to be more sensitive than both EtG and EtS [7].

This is a small study with several limitations. The sample size (n = 20) of the study limits the ability to generalize results. Patients were excluded from the study if they did not self-report at least two drinks/day five days a week. As demonstrated by this study, self-reporting is an unreliable measure of alcohol use. Enrollment for the study was a challenge. If a larger study is considered in the future, a more accurate screening process and altered inclusion criteria will need to be developed. Because of the cross-sectional study design, there are also several limitations including the inability to establish causality between EtOH use and chronic pain, several types of biases (Neyman bias, recall bias, and social desirability bias), and it is difficult to determine if the EtOH exposure measured by PEth levels were chronic exposure to EtOH or transient consumption events.

While it has been demonstrated that men often drink more alcohol than women, this study demonstrates a lower percentage than would be expected [19]. This may be, in part, attributable to the initial screening process excluding patients who did not self-report at least two drinks/day five days a week.

There was also a general hesitancy on the part of patients being screened for the study to participate in the study. While we did not collect data on the number of patients who declined to participate, the consensus among those involved in the study was that these numbers were significant. This may contribute to underreporting, as heavier EtOH use carries a degree of social stigma. It may be a significant factor, particularly among patients who signed an opioid agreement indicating they will not use EtOH and opioids.

There are some limitations associated with the PEth laboratory test. PEth can be affected by body mass index (BMI). There is an inverse relationship between PEth levels and BMI [20]. PEth is also affected by absorption and elimination of alcohol. This is associated with genetic factors, drinking pattern, rate of consumption, and stomach contents [3]. Phospholipase D (PLD) concentration and activity can also affect the rate of PEth formation, this can vary across individuals [21].

PEth is a promising biomarker for the detection of EtOH that may have the potential to increase safety for patients in chronic pain clinics. The current prevailing method of EtOH use detection in chronic pain clinics, self-report, is likely an inadequate measure of EtOH use. While there are some limitations with the PEth blood test it has proven to be very accurate at detecting EtOH use over a clinically relevant duration of time, with easy-to-interpret results. Further research on the use of the PEth test in the chronic pain setting is warranted.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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