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ORIGINAL ARTICLE

Toxicology

Load and go: Assessing safety outcomes of patients discharged from the emergency department after receiving phenobarbital for alcohol withdrawal

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This work, in part, has been presented at the Pennsylvania College of Emergency Physicians Scientific Assembly (May 5, 2023, Pocono Manor, PA) and the American College of Emergency Physicians Scientific Assembly (October 9, 2023, Philadelphia, PA). All authors have made substantial contributions to the case and endorse the paper and its conclusions.

Abstract

Objectives: Phenobarbital (PB) is a long-acting GABA A-agonist with favorable pharmacokinetics (long half-life and duration of effect) that allows effective treatment of alcohol withdrawal (AW) after administration of a single loading dose. Current evidence suggests that in the setting of AW, PB administration may be associated with decreased hospital admissions and hospital length of stay. The aim of this study was to evaluate the safety outcomes of AW patients who were treated and discharged from the emergency department (ED) after receiving PB for AW.

Methods: This retrospective chart review included a convenience sample of 33 AW patients who presented to four EDs within an 18-month span. Descriptive statistics (frequencies and percentages) were used to describe demographics, distribution of resources and referrals, and the safety outcomes of PB administration for low-risk AW patients. Patients were selected for inclusion in consultation with a medical toxicologist, treated with PB, and discharged from the ED. Electronic medical records were utilized to gather information on the patient cohort.

Results: All patients were treated with at least a single loading dose of 5–10 mg/kg (ideal body weight) of intravenous or per os PB during their ED stay. Only one patient had an unanticipated event after discharge, which was related to driving against advice. Two additional patients had ED revisits for recurrent alcohol use within 72 h, and 16 patients had recurrent alcohol use within 30 days. All 33 patients were provided with resources for linkage to treatment. None required hospital admission.

Conclusion: ED PB "load and go" may be a safe, effective AW treatment that could help treat AW, facilitate linkage to specific rehabilitation treatments, and decrease hospital admissions.

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KEYWORDS
phenobarbital, substance withdrawal, treatment outcome

1 | INTRODUCTION

1.1 | Background

Phenobarbital (PB) is a long-acting GABA A-agonist with a long half-life and duration of effect. These pharmacokinetics allow effective treatment of alcohol withdrawal (AW) after administration of a single loading dose.[1] Symptoms of alcohol withdrawal syndrome begin to manifest 8 h after the last drink and peak 24–72 h later.[2,3] Comparatively, in adults, the half-life of PB ranges from 53 to 118 h, with a mean of 79 h.[4] The long half-life of PB eases the burden of administration compared with benzodiazepines (BZDs), which may need to be given more than once per hour.[5] Although it has been used successfully as monotherapy in the inpatient setting for AW, the use of PB in AW patients discharged from the emergency department (ED) has not been widely studied.[6] Current evidence suggests that in the setting of AW, PB administration may be associated with decreased hospital admissions and hospital length of stay (LOS).[7,8] "Front-loaded" PB administration demonstrates both decreased rates of mechanical ventilation and need for continuous sedation, as well as a potential decrease in hospital and intensive care unit (ICU) LOS when prescribed in conjunction with BZD.[1,9] Phenobarbital usage is associated with a decreased likelihood of an ED return visit but other safety profile outcomes have not been well established.[10] Because of the efficacy of PB in decreasing hospital and ICU LOS and ED readmission, a subset of low-risk AW patients could be administered PB, linked with outpatient resources or medication-assisted treatment (MAT), and discharged from the ED ("load and go"). This approach allows for effective control of AW while allowing some patients to stay at home or be admitted to inpatient detoxification facilities rather than to inpatient hospital beds. The Prediction of Alcohol Withdrawal Severity Scale (PAWSS) (see the Supporting Information Appendix) accurately predicts moderate and severe AW.[11]

1.2 | Importance

The Division of Medical Toxicology and Addiction Medicine regularly utilizes a PB protocol to treat patients suffering from AW. These patients are routinely admitted to the hospital for several days due to the morbidity and mortality associated with AW. ED PB administration as a treatment for AW may be associated with decreased hospital admissions, decreased LOS, and decreased adverse outcomes.

1.3 | Goals of this investigation

This study's objective was to evaluate the safety outcomes and, specifically, unanticipated events and adverse outcomes of AW patients who were treated and discharged from the ED after receiving PB for AW.

2 | METHODS

2.1 | Study design, setting, and participants

This case series was approved by Lehigh Valley Health Network's Institutional Review Board and included a retrospective chart review and convenience sample of 33 patients who presented to one of four EDs in northeastern Pennsylvania between July 2021 and January 2023 with AW. PB for AW is a newer but accepted standard of care at this facility in the context of PB loading and discharge of symptomatic ED patients. By utilizing the PAWSS score and clinical acumen, toxicologists selected low-risk patients for PB dosing and discharge. The toxicology consult log was retrospectively reviewed to identify patients who received this treatment in the study time frame. While there may have been variability in the selection of patients for this treatment, the toxicologists did not include patients who had a history of withdrawal seizures, had delirium tremens, or had unstable vital signs. Due to the nature of design, there were no criteria that were applied that discriminated between BZD or PB dosing as a treatment method in this retrospective cohort study. Patients were selected for inclusion in consultation with a medical toxicologist and subsequently treated with 5–10 mg/kg (ideal body weight) intravenous (IV) or per os (PO) PB. The variation between a loading dose of 5 or 10 mg/kg or IV or PO was at provider discretion. Additionally, MAT, for example, naltrexone or acamprosate, was at the discretion of the toxicologist. The patients were (by standard work) observed for at least 1 h after final PB dose administration and then discharged from the ED either to home or an inpatient drug and alcohol rehabilitation facility. The sample cohort included patients with mild AW who declined or did not require admission and were dosed with PB to manage AW symptoms in the ED setting.

2.2 | Analysis

Electronic medical records were utilized to gather information on the patient cohort, including age, sex, race, presence of bedside medical

TABLE 1 Demographic variables one-way distribution.

	N	%
Age (years)		
21–30	6	18.2%
31–40	7	21.2%
41–50	11	33.3%
51–60	4	12.1%
61–80	5	15.2%
Sex		
Female	10	30.3%
Male	23	69.7%
Race		
Asian	1	3%
Caucasian	32	97%

toxicology consultation, PAWSS score, linkage to treatment, if the PB loading dose was given at MAT initiation, time from ED provider to discharge, disposition, patient return, follow-up instructions, interval to follow-up visit, type of follow-up, 30-day recovery status and unanticipated outcomes within 72 h of initial presentation (including adverse events [AEs] and unplanned hospital admissions). Specifically, examples of unanticipated outcomes for which the authors evaluated medical records included: adverse responses to PB during the visit (eg, allergic reaction), adverse outcomes following discharge, concerns about medical interaction with PB, or AEs related to the PB effects.

Descriptive statistics were provided for continuous and categorical variables (eg, age, PAWSS score, ED LOS, follow-up), which are presented as the means (±standard deviations) or medians with range of minimal and maximal values. Demographics, MAT initiation, distribution of resources and referrals, and safety outcomes were described as frequencies (*n*) and percentages (%). The software used to perform this analysis included SPSS v29.0.0.0 (IBM, 2022), MS Excel v2210, and R v4.1.2.

3 | RESULTS

The majority of patients were Caucasian (97%, $n = 32$), and 69.7% ($n = 23$) were male (Table 1). The median age was 43 years (Table 2). All patients were treated with a single loading dose of 5–10 mg/kg (ideal body weight) of IV or PO PB, and two patients received two additional doses of 32.4 mg PO during their ED stay. Regarding safety, one patient (3%) who resumed drinking after discharge had an unanticipated event (motor vehicle accident). The patient was evaluated in the ED at the second visit and discharged. Recurrence of alcohol use occurred in two patients (6.1%), resulting in a repeat visit to the ED within 72 h. Naltrexone was administered to eight patients (24.2%). Acamprosate was administered to two patients (6.1%). All 33 patients (100%) were provided with resources for linkage to treatment (Table 3), and 21 patients (63.6%) were referred for inpatient or outpatient treatment (Table 4).

The Bottom Line

This case series of 33 patients with moderate alcohol withdrawal were treated with a loading dose of phenobarbital prior to discharge from the emergency department. Adverse events were rare and often unrelated to the phenobarbital. This may be a safe and effective treatment for moderate alcohol withdrawal.

Only 15.1% of patients ($n = 5$) were identified as having followed up with an outpatient provider within the specified time window, and of these five patients, the median time from ED discharge to follow-up was 6 days (Table 2). The median PAWSS score was five, and the median time from seen by ED provider to discharge was 7 h (Table 2). At 30-day evaluation, 16 patients (48.5%) had recurrent alcohol use.

4 | LIMITATIONS

The data collected regarding the resources provided and who provided those resources, as well as barriers to care, were limited by a review of ED and medical toxicology documentation. The evaluation of patient outcomes and follow-up information was limited by review of data accessible in a single electronic medical record system. No direct patient follow-up was performed, so while there is electronic medical record documentation revealing recurrence of alcohol use in three patients within 72 h of PB load, no data are available regarding either how many additional patients may have consumed alcohol within a short duration after having received PB or if any experienced AE was not described in medical records. Also, very few patients were identified as having short-term outpatient follow-up; however, it is possible that more patients followed up with a provider or service that does not utilize the same available electronic medical records. Therefore, such follow-up information was not included in this retrospective review.

The small sample size of patients from four EDs within a single hospital network is a study limitation. Additionally, there was a selection bias in determining which patients the ED physician considered and medical toxicologists deemed appropriate for PB "load and go." Historically, at our institution, there is no minimum PAWSS score to receive PB, and PB is generally thought to be of potential benefit in patients with a PAWSS score of four or greater. There were no data collected regarding which patients were deemed inappropriate for PB administration or on those who received PB administration and were admitted. Differences in the actual dosing method (5 mg/kg vs. 10 mg/kg or PO vs. IV administration) were not evaluated in this small study. Physician discretion determined dosing; comorbidities such as chronic obstructive pulmonary disease, lower body weight, or lower blood pressure might have led a toxicologist to choose the lower dose or PO administration. Although ED physicians were instructed to speak with the medical toxicologist regarding patients whom they were considering a

TABLE 2 Means, standard deviations, medians, range, minimum and maximum values.

		Age	PAWSS score	Emergency department timeline (hours from provider to discharge)	When did the patient establish follow-up? (in days)
N	Valid	33	12	33	5
	Missing/NA	0	21	0	28
Mean		43.6	5.00	8.64	5.60
Median		43	5.00	7.00	6.00
Standard deviation		12.821	1.206	4.683	2.302
Minimum		25	3	3	2
Maximum		77	7	22	8

Abbreviation: PAWSS, Prediction of Alcohol Withdrawal Severity Scale.

TABLE 3 Distribution of types of resources provided.

	N	%
List of recovery treatment programs	15	45.5%
Referral to outpatient/inpatient	3	9.1%
List of recovery programs and referrals to outpatient or inpatient programs	12	36.4%
Referrals to outpatient or inpatient programs and recovery meetings	1	3%
List of recovery programs and referrals to outpatient or inpatient programs and recovery meetings	1	3%
List of recovery programs and referrals to outpatient or inpatient programs and tele-addiction services	1	3%

TABLE 4 Was the patient referred for treatment?

	N	%
Yes	21	63.6%
No	12	36.5%

PB "load and go," it is possible that patients were prescribed PB and subsequently discharged without contacting the medical toxicologist. Therefore, these patients were not included in this study.

5 | DISCUSSION

In this case series utilizing a novel approach of PB "load and go," there were no AEs observed in the ED, and no patients required admission due to PB administration. Although it is unclear how many patients in the cohort may have been admitted for treatment of AW symptoms if PB was not administered, none of these 33 patients required hospital admission. These results are commensurate with current literature suggesting that PB has relatively low rates of AE and can effectively and safely treat AW.[12] No patients in the case series PB cohort ($n = 33$) developed AW or AE compared to other literature, where 48% and 19% of patients developed AW or AE in the cohort ($n = 52$), respectively.[12] A recent meta-analysis demonstrated a similar decrease in hospital LOS with PB usage compared to BZD usage.[13]

In this case series, three patients returned to the ED within a short duration of time after PB administration. All patients had been instructed not to drive or drink alcohol for at least 7 days after receiving PB. All three patients returned with ethanol intoxication. In the future, more robust studies may evaluate whether there is an association between the medications offered at disposition for alcohol use disorder (AUD) after discharge and return rates. Future studies might also benefit from clarifying the length of time that driving restrictions should be advised.

While treatment of AW is a priority in the acute setting, linkage to treatment and offering MAT are also key for the long-term care and recovery of patients with AUD. Providing patients with resources for linkage to treatment and referral for outpatient or inpatient rehab is feasible from the ED. While ED providers may not be as familiar with MAT for AUD, review of these medications and screening for contraindications is easily performed in an ED setting in consultation with a medical toxicologist or addiction medicine specialist.

Further studies are needed to investigate the use of BZDs and PB in the context of post-discharge outcomes. The current evidence is mixed. Squibb et al evaluated 1602 patients with AW in a single-center retrospective cohort study and showed no differences in 30-day ED readmission when comparing PB to BZD.[14] Hawa et al evaluated 606 patients in a single-center retrospective cohort study and reported that PB had both lower readmission rates and fewer ED visits after discharge; however, the study was limited, with only 63 and 543 patients in the PB and BZD cohorts, respectively.[15]

ED PB "load and go" may be a safe, effective AW treatment that could help treat AW, facilitate linkage to specific rehabilitation treatments and decrease hospital admissions. Future studies with more robust patient follow-up and comparative design studies on patients

with AW who received alternate treatment to what we have described may provide additional safety and efficacy data, as well as further delineating effects on ED LOS and admission rates.

AUTHOR CONTRIBUTIONS

Conceptualization: Natalie E. Ebeling-Koning and Matthew D. Cook. *Data collection*: Natalie E. Ebeling-Koning, Alexandra M. Amaducci, Erin S. Smith, Ryan M. Surmaitis, Kenneth D. Katz, Andrew L. Koons, Derek J. Fikse, Matthew D. Cook, and Marna Rayl Greenberg. *Data analysis/critical review and evaluation of results*: Matthew Ferdock. *Writing and review/editing of the paper*: Natalie E. Ebeling-Koning, David Goodman, Alexandra M. Amaducci, Erin S. Smith, Ryan M. Surmaitis, Kenneth D. Katz, Andrew L. Koons, Derek J. Fikse, Matthew D. Cook, and Marna Rayl Greenberg. *Study supervision*: Matthew D. Cook and Marna Rayl Greenberg. *Procurement of grant or other funding*: Erin S. Smith and Andrew L. Koons. All authors had final approval of the version submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and addressed.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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