Results from the Implementation of a Hospital-wide IV based Phenobarbital Withdrawal Pathway

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Background

Alcohol is a significant contributor in up to 40% of all medical admissions and 50% of all surgical/trauma cases (Nisavic, 2019). Alcohol withdrawal treatment remains a challenge, given its association with agitation, overlap with other clinical presentations, and potential for delirium tremens which carries a 5-15% mortality rate if left untreated (Nisavic, 2019). While phenobarbital has been shown to be an effective treatment for alcohol withdrawal, including for general medical and surgical patients (Nisavic, 2019; Nejad, 2020), there remains a lack of consensus as to its use, and the vast majority of studies have been restricted to the intensive care unit (ICU) or emergency department (ED). Here, we present preliminary results from the implementation of a phenobarbital EMR-based order set designed for use across clinical locations.

Methods

- In January 2022, our institution, a 335-bed tertiary referral center, adopted a unified phenobarbital EMR-based order set. This order set expanded the use of IV phenobarbital from ICU/ED and Progressive Care Units (PCU) to the general medical wards. This order set used a weight-based dose-rounded 10 mg/kg (standard) or 5mg/kg (restricted use) IV phenobarbital load, followed by an "as needed" additional 5mg/kg linked to a bedside sedation scale. Medical providers, pharmacy and nurses were educated on its use.
- Use of locally stored premixed bags with "dose rounding" aimed to reduce delays in treatment.
- After obtaining IRB approval, data was extracted by EPIC report for patients presenting to the emergency department from 1/1/2021 to 9/13/2022 with either a diagnosis of alcohol abuse/dependence (F10 codes) OR use of a phenobarbital or lorazepam-based alcohol withdrawal order set.
- Tests to evaluate for statistical significance are shown in the charts to the right.

Table 1 Baseline pre/post protocol characteristics

Baseline	Pre-Protocol N=750	Post-Protocol N=471	P value
Male, n(%)	503 (67.1%)	311 (66.0%)	0.7083[a]
Age, mean±std*	54±13	55±12	0.8520[b]
Race, n(%):			0.0259[a]
Asian	10 (1.3%)	9 (1.9%)	
Black	23 (3.1%)	13 (2.8%)	
Hispanic	1 (0.1%)	3 (0.6%)	
White	705 (94.0%)	427 (90.7%)	
Other	11 (1.5%)	19 (4.0%)	
Race			0.0288[a]
White	705 (94%)	427 (90.7%)	
Non-White	45 (6%)	44 (9.3%)	
Phenobarbital Or Antiepileptic Drug Allergy, n(%)	26 (3.5%)	15(3.2%)	0.7901[a]
History Of Acute Intermittent Porphyria, n(%)	1(0.1%)	0(0%)	0.4279[a]
Cirrhosis, n(%)	21/750(2.8%)	12(471(2.6%)	0.7913[a]
Adjunct Therapy	271 (36.1%)	177 (37.6%)	0.6098[a]

*Std = Standard deviation [a]Chi-Square Test [b]Unpaired T-Test

Table 2 Effects of phenobarbital protocol on drug administration

Drug	Pre-Protocol N=750	Post-Protocol N=471	P value
Benzodiazepines (%)	412 (54.9%)	194 (41.2%)	<.0001[a]
Phenobarbital (%)	31 (4.1%)	98 (20.8%)	
Both (%)	27 (3.6%)	61 (13.0%)	
None (%)	280 (37.3%)	118 (25.0%)	
Received any Benzo and/or Phenobarbital (%)	470 (62.7%)	353 (75%)	<.0001[a]
Any Phenobarbital	58/750(7.7%)	159/471(33.8%)	<.0001[a]
Any Benzodiazepine	439/750(58.5%)	255/471(54.1%)	0.1314[a]
Minutes from PHB Order To Administration,median (IQR*)	186(59-470)	36(18-63)	<.0001[b]
Phenobarbital Level	NA	10.6±5.1 n=130 available data	NA

*Interquartile Range [a]Chi-Square Test [b]Wilcoxon Rank Sum test

Table 3 Baseline characteristics within post-protocol 471 patients: comparing benzo vs phenobarbital received by patients

Baseline	Benzo N=194	Phenobarb N=98	P value
Male, n(%)	115(59.3%)	71(72.5%)	0.0271[a]
Age, mean±std*	53±15	52±13	0.7140[b]
Race, n(%):			0.5840[a]
Asian	4(2.1%)	1(1.0%)	
Black	6(3.1%)	1(1.0%)	
Hispanic	2(1.0%)	0(0%)	
White	176(90.7%)	92(93.9%)	
Other	6(3.1%)	4(4.1%)	
Phenobarbital Or Antiepileptic Drug Allergy, n(%)	7(3.6%)	3(3.1%)	0.8082[a]
History Of Acute Intermittent Porphyria, n(%)	0(0%)	0(0%)	NA
Cirrhosis, n(%)			0.1634[a]
Not Noted	187(96.4%)	96(98.0%)	
Noted before OrserSet	7(3.6%)	1(1.0%)	
Noted after OrderSet	4(0.5%)	1(1.0%)	

Std*: Standard deviation [a]Chi-Square Test [b]Unpaired T-Test

Table 4 Benzodiazepine vs phenobarbital post-protocol

Outcomes	Benzo N=194	Phenobarb N=98	P value
Delirium, any point (%)	9/194(4.6%)	10(10.2%)	0.0687[a]
Delirium(Noted after OrderSet), n/N(%)	3/194(1.6%)	3/98(3.1%)	0.3889[a]
Seizures, any point (%)	6/194(3.1%)	2/98(2.0%)	0.6031[a]
Length Of Stay (hrs),median(IQR*)	73(22-125)	88(55-173)	0.0034[b]
Length Of Stay (hrs),median(IQR*)			
Female	92(50-155)	104(71-199)	0.2408[b]
Male	57(18-119)	75(49-155)	0.0010[b]
Length Of Stay As Emergency Class (hrs), median (IQR*)	6(4-12)	4(2-5)	<.0001[b]
Length Of Stay In Emergency Department (hrs)	12(7-21)	7(4-14)	<.0001[b]
ICU admission, n(%)	11/194(5.7%)	13/98(13.3%)	0.0257[a]
Length Of Stay In ICU (hrs)	336(180-1095)	362(190-752)	0.8620[b]
Discharge Disposition: n(%)			0.2484[a]
Expired	3 (1.6%)	3 (3.1%)	
Home	136 (70.1%)	77 (78.6%)	
Rehab	9 (4.6%)	5 (5.1%)	
Skilled nursing	16 (8.3%)	3 (3.1%)	
Other	30 (15.4%)	10(10.1%)	
Mortality, n(%)	3/194(1.6%)	3/98(3.1%)	0.3889[a]
Intubation After Order Set Initiation	0/194(0%)	2/98(2.0%)	0.0459[a]

*Interquartile Range [a]Chi-Square Test [b]Wilcoxon Rank Sum test

Results

- Examination of baseline characteristics between pre- and post-protocol groups (**Table 1**) showed the groups as comparable in terms of sex, age and history of conditions making phenobarbital contraindicated. There was a statistically significant (though small absolutely) increase in non-white population after implementation.
- Overall, more patients post-protocol than pre-protocol received any GABA-based treatment for alcohol withdrawal (75% vs 62.7%, $p < 0.0001$, **Table 2**).
- Implementation of the protocol caused a rapid increase in the percent of alcohol withdrawal patients receiving phenobarbital (**Table 2**, 33.8% vs 7.7%, $p < 0.0001$).
- Importantly, the "time to drip" from order to administration for phenobarbital reduced from 186m (59-470m) to 36m (18-63m), $p < 0.0001$ (**Table 2**).
- Examination of the baseline characteristics between post-protocol "benzo" and "phenobarbital" groups (**Table 3**) showed a higher percentage of males received phenobarbital compared with females (72.5% vs 59.3%, p=0.0271).
- While length of stay (LOS) in the ED was reduced for patients with phenobarbital from 12 (7-21) hrs to 7 (4-14) hrs (**Table 4**, $p < 0.0001$), the LOS for hospitalization was increased, likely driven by the increase in ICU admissions.
- There was no statistical change in delirium, seizure incidence or mortality (**Table 5**).

Discussion

- This protocol successfully shifted our institution's prescribing pattern for alcohol withdrawal treatment, with a five-fold increase in the percentage of patients receiving phenobarbital.
- Our protocol drastically reduced the "time to drip" for phenobarbital, an important metric in an often agitated population.
- Our data suggests prescribing trends that require further investigation: men were more likely to receive phenobarbital, and the increased LOS in the phenobarbital group is hypothesized to represent a prescribing trend of a sicker patient population receiving phenobarbital.

Conclusions and Next Steps

- IV phenobarbital was successfully implemented on med/surg floors with rapid uptake in use
- Our use of premixed bags allowed for quicker administration
- Further subanalyses are needed to clarify prescribing patterns and effects on LOS

References

Nisavic M et al: Use of Phenobarbital in Alcohol Withdrawal Management: A Retrospective Comparison Study of Phenobarbital and Benzodiazepines for Acute Alcohol Withdrawal Management in General Medical Patients. Psychosomatics 2019; 60:458-467.
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