UAMS Journal Club Summary
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Outcomes of patients in alcohol treated with Phenobarbital vs Lorazepam

Clinical Bottom Line

Phenobarbital alone and Lorazepam plus Librium were similarly effective in the ED treatment of mild to moderate, acute alcohol withdrawal with respect to symptom control, length of stay, treatment failures, and symptoms at 48hours though sample sizes were small and some of the methodology was unusual. This may be an option for admitted patients, but given the long half life, we would be reluctant to load a patient with phenobarbital and then discharge them from the ED without higher quality studies.

PICO Question

P- Patients presenting to ED with alcohol withdrawal
I- phenobarbital
C- benzodiazepines
O- Change outcomes such as symptom severity, disposition, and ED length of stay

Background

Ethanol is the most frequently abused intoxicant in our society, and alcohol overuse is among the leading causes of mortality and morbidity in the United States, with more than 200,000 alcohol related deaths occurring each year. Emergency Physicians diagnose and treat alcohol related illness on a daily basis. One of the most common presenting complications related to alcohol abuse is Acute Alcohol withdrawal syndrome (AW). It is associated with significant morbidity and resource utilization. It is characterized by a hyper-autonomic state that can range in severity from mild tremor or tachycardia to significant confusion and severe seizures. Most often, symptoms peak in intensity at 48hrs after their last alcohol intake. Currently the first line medications to treat AW are benzodiazepines, Lorazepam being the most common choice. A large portion of patients with AW are discharged with prescriptions for a tapering course of benzodiazepines. This can lead to further complications such as non-compliance, overdose, or concomitant use with alcohol or other drugs leading to dangerous over-sedation. More severe patients are often treated with large amounts of benzodiazepines increasing risk of adverse drug reactions and longer length of hospital stay. Phenobarbital has been used for decades and prior to development of benzodiazepines was once the preferred treatment of AW. Due to these complications, physicians and scientists have proposed the reintroduction of phenobarbital as another treatment for alcohol withdrawal in the modern Emergency Department.

Trial 1

Gregory W. Hendey, Robert A. Dery, Randy L. Barnes, Brandy Snowden, Philippe Mentler**.** *A prospective, randomized, trial of phenobarbital versus benzodiazepines for acute alcohol withdrawal***.** The American Journal of Emergency Medicine**,** Volume 29, Issue 4, 2011, Pages 382-385, ISSN 0735-6757, https://doi.org/10.1016/j.ajem.2009.10.010**.**

Pubmed link: https://www.ncbi.nlm.nih.gov/pubmed/20825805

Validity Rating: low to moderate risk of bias, sample size is low and many lost at 48 hours
The Basics:
Prospectively, randomized, consenting patients were assessed using a modified Clinical Institute Withdrawal Assessment (CIWA) score and given intravenous Phenobarbital (mean, 509mg) or Lorazepam (mean, 4.2mg). At discharge Lorazepam patients recieved chlordiazepoxide (Librium) and Phenobarbital patients received placebo.

Inclusion Criteria:
Adults ≥18 years of age
Only patients with symptoms of Alcohol withdrawal in habitual alcohol users
Only patients in whom treating physician considered management of alcohol withdrawal with parenteral benzodiazepine or phenobarbital were included

Exclusion Criteria:
Patients unable to give informed consent.
Patients under influence of other drugs
Patients less than 18 years of age

Primary Outcomes:
Change in alcohol withdrawal (modified CIWA) score in each group from ED baseline to discharge or admission score

Secondary Outcomes:
Difference between groups after treatment
-ED LOS
-percentage of each group admitted to hospital
-number of doses and total dose of treatment
-percentage who sought additional medical treatment after ED discharge
-change in AW scores from ED baseline to 48hour reassessment

Follow Up:

Data was extracted from the electronic medical record on standardized study forms and entered into Microsoft Excel spreadsheets. Study endpoint was at time of discharge or admission.

Results:
Of 44 patients, 25 received phenobarbital (PB) and 19 lorazepam (LZ). Both PB and LZ reduced CIWA scores from baseline to discharge. (15.0-5.4 and 16.8-4.2, P<0.0001). There were no differences between PB and LZ in baseline admissions (12% versus 16%, P=0.8), or 48hr follow up CIWA scores (5.8 versus 7.2, P=0.6)

Limitations/Bias:
-Single center study
-small sample size
-too underpowered to detect meaningful differences in subgroup analyses or between groups at 48hour follow up
-patient follow up at 48hrs was poor
-study only enrolled patients with mild to moderate alcohol withdrawal and thus findings cannot be generalized to more severe cases
-study can only comment on Lorazepam, other benzodiazepines not studied
-the population of patients who followed up reported low relapse rate and high rate of compliance with outpatient medications, this finding is possibly affected by reporting bias

Trial 2

Jonathan Rosenson, Carter Clements, Barry Simon, Jules Vieaux, Sarah Graffman, Farnaz Vahidnia, Bitou Cisse, Joseph Lam, Harrison Alter. *Phenobarbital for Acute Alcohol Withdrawal: A Prospective Randomized Double-blind Placebo-controlled Study*. The Journal of Emergency Medicine. Volume 44, Issue 3, 2013, pp 592-598.e2, ISSN 0736-4679, https://doi.org/10.1016/j.jemermed.2012.07.056.

Pubmed link: https://www.ncbi.nlm.nih.gov/pubmed/22999778

Validity Rating:
- Internal validity: low to moderate risk of significant bias - their method of waiving consent is concerning, sample size probably too small, providers had input on the primary outcome
- External: ED patients >18 who are not pregnant and don't have known severe hepatic impairment requiring hospital admission primarily for alcohol withdrawal

The Basics:

- In an urban ED, between Jan 2009 and March 2010, 460 patients presented to ED with acute alcohol withdrawal. 198 enrolled in the study and 102 met inclusion criteria. 51 randomized to phenobarbital and 51 to placebo and there were no baseline differences between the two groups. Randomization was done by the pharmacy department using a random number generator. The pentobarbital group received one dose of 10mg/kg of phenobarbital in a 100 ml bag NS over 30 min and then placed on a modified version of CIWA. The placebo group received 100 ml NS over thirty minutes and were placed on a modified CIWA. Both patients and providers were blinded.

Exclusion Criteria:

- Age <18
- Pregnancy
- Allergy to phenobarbital, lorazepam, phenytoin, or carbamazepine
- Known severe hepatic impairment
- Inability to obtain IV access
- Preliminary admission diagnosis other than alcohol withdrawal

Inclusion Criteria:

- Clinical evidence of acute alcohol withdrawal syndrome: including tachycardia >100, tremor, paroxysmal sweats, agitation, anxiety, hallucinations, or clouded sensorium
- Provider judgement of clinical need for placement on the institutional lorazepam-based alcohol withdrawal protocol
- Clinical judgement of anticipated need for hospital admission for inpatient management of acute alcohol withdrawal syndrome

Primary Outcomes:

- Initial level of hospital admission from the ED: ICU, telemetry, floor/ward

Secondary Outcomes:

- Use of continuous lorazepam infusion
- Length of hospital stay
- Total amount of lorazepam used per patient
- Incidence of adverse events (seizures, intubations, falls, use of mechanical restraints, need for sitter, mortality)

Follow Up:

- Data extracted from EMR/chart
- Pharmacy dept extracted medication data from hospital pyxis system
- All data recorded on a standardized data collection instrument and stored in Excel

Results:

- Phenobarbital group had a decreased ICU admission rate (8% vs 25% [95% CI 4-32%])
    - No difference in telemetry admission or floor/ward admission

- Phenobarbital resulted in decreased use of continuous lorazepam infusion (4% vs 31% [95% CI 14-41%]) and total lorazepam required (26mg vs 49mg [95% CI 7-40])
- No difference in ICU LOS or total hospital LOS
- No difference in administration of other medications, including morphine, fentanyl, hydromorphone, propofol or haloperidol
- No difference in adverse events between groups
    - Note: no mortality in either group

Limitations/Bias

- Single center
- Small study, low power for detecting significant differences
- Did not use CIWA-A but an institution-specific variant, details not discussed.
- Not a phenobarbital monotherapy vs lorazepam monotherapy trial
- Patient who were initially too altered to provide consent were waived consent, entered in the study and then consented later, once they regained capacity.
- Patients could have unblinded themselves by recognizing they were receiving phenobarbital if they had received it in the past.
- Decision to admit patient to floor vs ICU vs telemetry was based on provider judgement rather than a standard protocol