

## Weekly Pharmacy Pearl: Phenobarbital for Alcohol Withdrawal

### Background

- Benzodiazepines are standard of care in the management of alcohol withdrawal. They increase the frequency of chloride channel opening on GABA receptors<sup>4</sup>
  - Diazepam
    - Onset: 1-5 min IV
    - Half-life: 43 hours
  - Lorazepam
    - Onset: 5-20 min IV
    - Half-life: 14 hours
- Some patients with alcohol use disorder become GABA depleted. **Benzos will not produce any effect in the absence of endogenous GABA.**
- These patients develop **benzodiazepine resistant alcohol withdrawal** defined as either:
  - $\geq 40$ -50 mg IV diazepam in 1 hour
  - $\geq 200$  mg diazepam in 4 hours<sup>2</sup>
- In this subset of patients, the use of phenobarbital may be advantageous due to:
  - Increase in frequency of channel opening
  - Activation of GABA receptors without endogenous GABA
  - Inhibition of NMDA and AMPA receptors

### Phenobarbital Kinetics

- Onset: 5 minutes
- Peak: 20-30 minutes
- Half-life: 3-4 **days**

### Dosing Regimens

- Studied as both monotherapy and as adjunct to benzodiazepines
- Initial load (lower doses than for status epilepticus):
  - 10 mg/kg IV over 30 minutes<sup>3</sup> followed by symptom-triggered benzodiazepine protocol
    - In a randomized prospective double blind active comparator trial to standard symptom triggered lorazepam protocol, phenobarbital load upfront did not have increased incidence of respiratory depression or need for intubation compared to standard of care
      - 1 patient in both the phenobarb group (n =51) and the lorazepam group (n=51)required intubation
- Intermittent boluses
  - 65 mg, 130 mg, or 260 mg boluses every 30 minutes (max cumulative dose of 10 mg/kg)
  - Usually, initial dose is either 260 mg or 130 mg, with subsequent boluses either 130 mg or 65 mg depending on repeat CIWA-Ar score

## Recommendation

Consider IV load of 10 mg/kg phenobarbital upfront in:

- Previously documented admissions for EtOH withdrawal that required  $\geq 40$ -50 mg diazepam equivalents within the first hour
- At risk patients for severe or complicated alcohol withdrawal<sup>1</sup>
  - History of alcohol withdrawal delirium or seizures due to alcohol withdrawal
  - Numerous prior withdrawal episodes in patient's life
  - Comorbid medical illness (esp. traumatic brain injury)
  - Age  $\geq 65$
  - Long duration of heavy and regular alcohol consumption
  - Seizure during current withdrawal episode
  - Marked autonomic hyperactivity on presentation
  - Physiologic dependence on GABAergic agents like benzodiazepines or barbiturates
- Patients requiring hospital admission

Consider intermittent bolus strategy in moderate to severe alcohol withdrawal if:

- Requiring frequent/escalating doses of benzodiazepines
- Consider lower doses of 65 mg or 130 mg in withdrawal with BAL > 100
- Once CIWA < 10, continue with standard symptom triggered benzodiazepine protocol

## References

1. 2020 ASAM Clinical Practice Guideline on Alcohol Withdrawal Management.
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3. Rosenson, J., Clements, C., Simon, B., Vieaux, J., Graffman, S., Vahidnia, F., Cisse, B., Lam, J., & Alter, H. (2013). Phenobarbital for acute alcohol withdrawal: A prospective randomized double-blind placebo-controlled study. *Journal of Emergency Medicine*, 44(3). <https://doi.org/10.1016/j.jemermed.2012.07.056>
4. Nisavic, M., Nejad, S. H., Isenberg, B. M., Bajwa, E. K., Currier, P., Wallace, P. M., Velmahos, G., & Wilens, T. (2019). 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*, 60(5), 458–467. <https://doi.org/10.1016/j.psym.2019.02.002>
5. Nelson, A. C., Kehoe, J., Sankoff, J., Mintzer, D., Taub, J., & Kaucher, K. A. (2019). Benzodiazepines vs barbiturates for alcohol withdrawal: Analysis of 3 different treatment protocols. *American Journal of Emergency Medicine*, 37(4), 733–736. <https://doi.org/10.1016/j.ajem.2019.01.002>
6. Lebin, J. A., Mudan, A., Murphy, C. E., Wang, R. C., & Smollin, C. G. (2022). Return Encounters in Emergency Department Patients Treated with Phenobarbital Versus Benzodiazepines for Alcohol Withdrawal. *Journal of Medical Toxicology*, 18(1), 4–10. <https://doi.org/10.1007/s13181-021-00863-2>