Phenobarbital for Severe Alcohol Withdrawal

Introduction

1. Alcohol withdrawal syndrome (AWS) is a disease commonly treated in the emergency department, with ~5% of cases leading to delirium tremens..
2. In patients with a history of AWS, decreased GABA-A receptor sensitivity to GABA agonists may cause benzodiazepine (BZD) monotherapy to be ineffective.
3. Patients may experience increase in morbidity and mortality due to escalated doses of benzodiazepines.
4. There are likely a subset of patients that respond poorly to benzodiazepines, therefore requiring alternative mechanisms to treat AWS.
5. Phenobarbital (PB) has some theoretical benefits over benzodiazepines alone from a mechanistic perspective.
    a. Chronic alcohol use leads to down regulation of GABA-A receptors and up-regulation of NMDA receptors.
    b. Abrupt withdrawal of alcohol use leads to greater NMDA receptor mediated excitatory activity, which may be inhibited more effectively with phenobarbital rather than benzodiazepines.

Pharmacology	
	Phenobarbital
Dose	**Prior to benzodiazepines** • 5-10 mg/kg over 30 minutes o Can split up into multiple doses if concerned about respiratory depression **After receiving benzodiazepines** • 130-260 mg PRN Q30 minutes to clinical effect (Max ~10-15 mg/kg)
Mechanism of Action	Bind to the GABA receptor at a different binding site than BZDs, increasing the time the GABA-mediated chloride channels remain open • Inhibitor of excitatory AMPA glutamates receptors
Formulations	IV/IM/PO
PK/PD	Onset: IV ~5 minutes Duration: 6-12 hours Half-life: 80-120 hours Renal Excretions: 21% Therapeutic Blood levels: 15-40 ug/mL
Drug Interactions and warnings	Warning with loading doses in patients that are hypotensive and received large doses of benzodiazepines
Compatibility	Compatible with NS, D5W, and LR
Adverse Effects	Hypotension, respiratory depression, ataxia, lethargy

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Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Pourman A, 2023	Meta-Analysis N=1934	Phenobarbital compared with benzodiazepines.	○ **No difference in intubations, seizures, and length of stay**
Ibarra, 2019	Retrospective observational/ n=78	Lorazepam protocol only (LZP) PB x 1 + LZP protocol (PB+LZP)	○ **No difference in daily lorazepam requirements or hospital LOS** ○ **PB+LZP group had ↑ pts d/c within 72 hrs** ○ No patient in PB group experienced intubation or hypotension
Nisavic, 2019	Retrospective observational/ n=562	BZD only fixed dosing PB- Based Protocol (IM load + PO taper)	○ **No difference in AWS-related seizures, ICU admission, oversedation, LOS, and hallucinations** ○ ↑ Delirium in BZD group ○ **In BZD→PB crossover pts, PB led to rapid improvement of BZD resistant AWS symptoms**
Nelson, 2019	Pre-post observational/ n=300	IV diazepam alone (DZP) IV LZP + IV PB (LZP + PB) IV PB alone (PB)	○ **No difference in ICU admission, ICU LOS, and need for intubation.** ○ PB associated with ↑ ED LOS but ↓ BZD requirements
Tidwell, 2019	Pre-post observational/ n=120	BZD only CiWA- Protocol PB Taper ± Benzo PRN	○ **PB ↓ ICU+ Hospital LOS** ○ PB ↓ total lorazepam requirements ○ PB had less patient intubated
Sullivan, 2018	Retrospective observational/ n=209	BZD only CIWA- Protocol PB + BZD CIWA Protocol	○ **No difference in ICU admission, intubation, hypotension, ED LOS, CIWA score at ED discharge** ○ PB group had ↓ hospital LOS and Max CIWA score at 24 hrs
Rosenson, 2013	RCT/ n=102	PB 10 mg/kg IV x1 + PRN benzodiazepines Placebo + PRN benzodiazepines	○ **PB had ↓ ICU admission** ○ PB had ↓continuous infusion lorazepam ○ PB had ↓ total lorazepam requirements ○ No difference in ICU or hospital LOS

BZD= Benzodiazepines, DZP= diazepam, ED= emergency department; ICU=Intensive care unit; LOS=length of stay; LZP=lorazepam; PB= Phenobarbital; ↓= statistically significant decreased; ↑= statistically significant increased

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