Phenobarbital: Monotherapy for Alcohol Withdrawal Treatment

ArnotHealth

Principal Investigators: Sumyyah Yousufi, DO,MBA, Manav Bandlamudi,MD, Vidhya Reddy, MD, Kara Finegan, DO, Dr. Wicelinski, DO

Abstract

Alcohol related deaths are the fourth leading cause of preventable deaths in the United States. Chronic ingestion of ethanol causes a down regulation of GABA receptors, and up regulation of excitatory Glutaminergic receptors. If ethanol is not present, the lack of sufficient inhibitory neurotransmitter activity leads to the fatal consequence of Alcohol Withdrawal Syndrome (AWS including Delirium Tremens (DT).

The standard of care for AWS and DT's has been Benzodiazepines in conjunction with the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scale for many years, but recent studies suggests that Phenobarbital (PB) maybe superior when treating AWS since it simultaneously enhances GABA activity and suppresses Glutaminergic activity. In contrast, Benzodiazepines (BZD) can promote agitated delirium, have shorter half lives thus require more frequent dosing, and work only by stimulating inhibitory GABA receptors.

This study will help determine if using Phenobarbital instead of Benzodiazepines reduced the frequency of medication administration and subsequent length of stay.

Background

Benzodiazepines have been the mainstay of treatment for AWS In the recent years, Phenobarbital has emerged as a possible option for monotherapy for AWS. Unfortunately, the only prospective study that has compared Phenobarbital to Benzodiazepines for treatment of Delirium Tremens in Kramp, 1978. The study concluded that Phenobarbital was superior to Benzodiazepines for complete treatment of DTs.

Over the past two years, several studies have been conducted. Though they were not large studies, they have illustrated interesting perspectives. One of which was conducted by Tidwell et al compared hospital length of stay and other factors while using PB and BZD

Outcome or clinical characteristic	CIWA-Ar arm (n=60)	Phenobarbital arm (n=60)	P
ICU stay (midnights), mean (SD)	4.4 (3.9)	2.4 (1.5)	<.001
Hospital stay (midnights), mean (SD)	6.9 (6.6)	4.3 (3.4)	.004
Total lorazepam equivalents, mean (SD), mg	35.2 (48.5)	11.3 (18)	<.001
Ventilator use, No. of patients	14	1	<.001
Dexmedetomidine use, No. of patients	17	4	.002
Olanzapine use, No. of patients	7	5	.54
Haloperidol use, No. of patients	10	4	.08
Quetiapine use, No. of patients	5	2	.24

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; ICU, intensive care unit.

Figure 1: (Above) Results of a study showing superiority of a PB protocol over a BZD AWS (Tidwell WP et al. 2017)

Phenobarbital vs. Benzodizepines in AWS

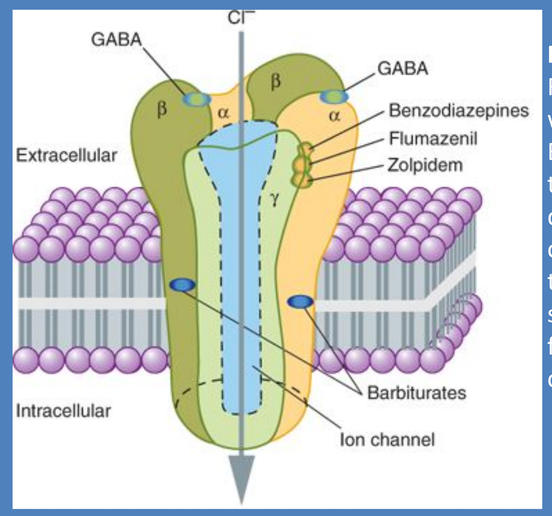

Figure 2: (Left) GABA Receptor illustrated with multiple Barbiturate binding sites that increase the duration of chloride channel opening versus the single BZD binding site that increases the frequency of chloride channel opening.

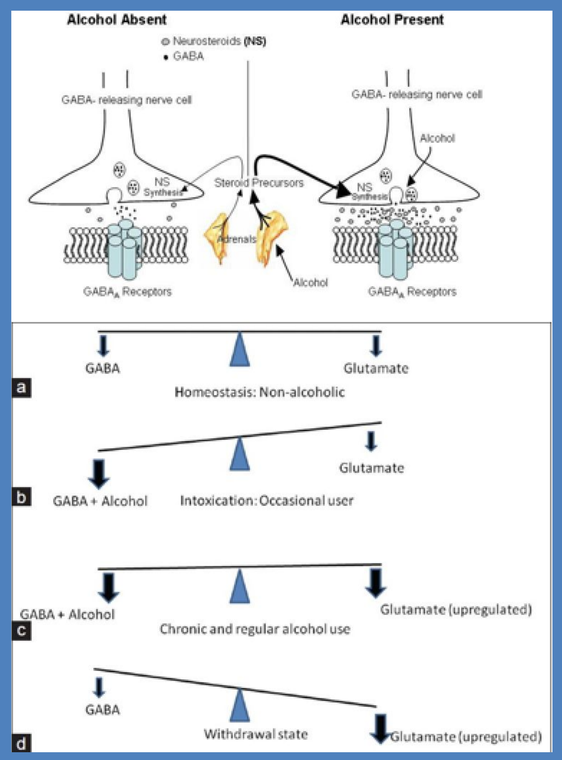

Figure 3: (Right)Illustration of changes that occur with chronic alcohol use. Chronic consumption of alcohol, down regulates GABA-receptors in order to maintain homeostasis. There is a compensatory up regulation of excitatory, Glutamate. When alcohol is not present. GABA receptors are so insensitive to GABA that the typical amount of GABA produced has little effect. In combination with the fact that GABA is inhibitory, sympathetic activation is unopposed!

Materials and Methods

To establish a control group, an initial search to retrospectively study subjects with a ICD 10 coding for AW (F10.239) or ICD 10 Coding for AW delirium (F10.231) from January 2018- January 2019. Data will be collected on: the initial CIWA score, the amount of medication administered in total, the LOS in hospital, and if the patient needed intubation. Upon implementation of the protocol, subjects that have been treated with Phenobarbital will be prospectively recruited. The data collected will be the same as the control group.

Emergency department physicians and the Internal Medicine resident teams will assess the patient with the CIWA scale and order the appropriate Phenobarbital dosing.

- CIWA >15: 260 mg of Phenobarbital IVP
- CIWA 10-15: 130 mg of Phenobarbital IVP
- CIWA 8-10: 65 mg of Phenobarbital IVP

The patient will be monitored closely and re-dosed if desired effect (Richmond Agitation-Sedation Scale of -1 to 0) is not reached.

When the patient has not required any doses of phenobarbital for 24 hours, further management can be continued outside of the ICU. At that time, a Phenobarbital taper should be initiated as described below:

Day 1: 60mg 4x a day
Day 2: 60mg 3x a day
Day 3: 60mg 2x a day
Day 4: 30mg 2x a day

Conclusion/Data

Data and conclusion pending.