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Original Contributions

PHENOBARBITAL FOR ACUTE ALCOHOL WITHDRAWAL: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

Jonathan Rosenson, MD,* Carter Clements, MD,* Barry Simon, MD,* Jules Vieaux, BS,† Sarah Graffman, RN,* Farnaz Vahidnia, MD, MPH,*‡ Bitou Cisse, BA,* Joseph Lam, PHARMD,§ and Harrison Alter, MS, MD*

*Department of Emergency Medicine, Alameda County Medical Center/Highland Hospital, University of California, San Francisco School of Medicine, Oakland, California, ‡Division of Epidemiology and Biostatistics, University of California, Berkeley, Berkeley, California, †University of California, Davis School of Medicine, Sacramento, California, and §Pharmacy Department, Alameda County Medical Center/Highland Hospital, Oakland, California

Reprint Address: Jonathan Rosenson, MD, Department of Emergency Medicine, Alameda County Medical Center/Highland Hospital, 1411 E. 31st Street, Oakland, CA 94602

☐ **Abstract—Background: Acute alcohol withdrawal syndrome (AAWS) is encountered in patients presenting acutely to the Emergency Department (ED) and often requires pharmacologic management. Objective: We investigated whether a single dose of intravenous (i.v.) phenobarbital combined with a standardized lorazepam-based alcohol withdrawal protocol decreases intensive care unit (ICU) admission in ED patients with acute alcohol withdrawal. Methods: This was a prospective, randomized, double-blind, placebo-controlled study. Patients were randomized to receive either a single dose of i.v. phenobarbital (10 mg/kg in 100 mL normal saline) or placebo (100 mL normal saline). All patients were placed on the institutional symptom-guided lorazepam-based alcohol withdrawal protocol. The primary outcome was initial level of hospital admission (ICU vs. telemetry vs. floor ward). Results: There were 198 patients enrolled in the study, and 102 met inclusion criteria for analysis. Fifty-one patients received phenobarbital and 51 received placebo. Baseline characteristics and severity were similar in both groups. Patients that received phenobarbital had fewer ICU admissions (8% vs. 25%, 95% confidence interval 4–32). There were no differences in adverse events. Conclusions: A single dose of i.v. phenobarbital combined with a symptom-guided lorazepam-based alcohol withdrawal protocol resulted in decreased ICU admission and did not cause increased adverse outcomes.** © **2013 Elsevier Inc.**

☐ **Keywords—alcohol withdrawal; emergency medicine; ICU; lorazepam; phenobarbital**

INTRODUCTION

Background

Small studies have investigated use of phenobarbital for treatment of acute alcohol withdrawal (1–3). The longer half-life of phenobarbital compared to lorazepam may be a clinical advantage in the treatment of acute alcohol withdrawal (4). The lack of prospective data regarding use of phenobarbital for alcohol withdrawal leaves clinicians basing their use of phenobarbital for acute alcohol withdrawal on limited or anecdotal evidence.

Importance

Acute alcohol withdrawal is encountered in patients presenting acutely to the Emergency Department (ED). There are likely in excess of 8 million alcohol-dependent people in the United States; every year, approximately 500,000 episodes of acute alcohol withdrawal syndrome (AAWS) require pharmacologic management (5). AAWS results in a significant utilization of health care resources,

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particularly in safety-net and emergency health care settings.

Goals of This Investigation

We hypothesized that a single dose of intravenous (i.v.) phenobarbital combined with a standardized, symptom-guided lorazepam-based alcohol withdrawal protocol would result in decreased intensive care unit (ICU) admission.

MATERIALS AND METHODS

Study Design

This was a prospective, randomized, double-blind, placebo-controlled study of ED patients with AAWS admitted to the hospital with a primary admission diagnosis of alcohol withdrawal (International Classification of Diseases, 9th Revision [ICD-9] code 291.81). All study investigators, enrolling providers, nursing staff, statisticians, and research assistants were blinded to group allocation for the duration of the study. Unblinding occurred after completion of data analysis. The study institution Committee for the Protection of Human Subjects and study investigators produced a consent procedure based on prior studies investigating treatment of AAWS and associated complications (6,7). The study Institutional Review Board (IRB) approved the study (ClinicalTrials.gov NCT 01884417).

Setting

The study took place in an urban ED with an annual census of 85,000 patients and a postgraduate year 1–4 Emergency Medicine residency program with 17 attending Emergency Physicians, 12 ED mid-level practitioners (MLPs), and 40 Emergency Medicine residents.

Selection of Participants

All patients over age 18 years presenting to the ED with suspected AAWS were evaluated by the enrolling attending Emergency Physician, MLP, or resident for participation in the study (all MLPs and residents were supervised by an attending Emergency Physician, and all patients were evaluated and examined by the attending physician). Inclusion criteria included provider judgment of clinical need for placement on the institutional lorazepam-based alcohol withdrawal protocol, clinical evidence of AAWS (including tachycardia [heart rate >100 beats/min], tremor, paroxysmal sweats, agitation, anxiety, hallucinations, or clouded sensorium) and provider judgment of anticipated need for hospital admission for inpatient management of AAWS (primary admission diagnosis ICD-9 Code 291.81). The study took place between January 2009 and March 2010 (Figure 1).

Exclusion criteria included age <18 years; pregnancy; allergy to phenobarbital, lorazepam, phenytoin, or carbamazepine; known severe hepatic impairment; inability to obtain i.v. access; and primary admission diagnosis other than acute alcohol withdrawal (ICD-9 Code 291.81).

Written informed consent was obtained from all study participants using a standardized consent form. Consent was initially waived for patients who were unable to give informed consent at the time of presentation due to intoxication or altered mental status. Once the patient became alert and demonstrated decision-making capacity, written consent was required for the continued collection of data; a post-waiver consent form was made available to these patients for this purpose. The rationale for waiver of initial consent is that all patients presenting with AAWS who were enrolled in the study were placed on the institution's lorazepam-based alcohol withdrawal protocol, an accepted standard-of-care treatment strategy for management of AAWS regardless of administration of additional agents used in the management of AAWS, such as phenobarbital or normal saline (8). Additionally, our institutional lorazepam-based alcohol withdrawal protocol is typically initiated without special consent of patients placed on the protocol for AAWS.

Randomization occurred in the Pharmacy Department using a random number-generator program without block randomization.

Interventions

All study participants were placed on the institutional symptom-guided lorazepam-based alcohol withdrawal protocol, a modified version of the Clinical Institute Withdrawal Assessment (CIWA) protocol. This protocol is applied globally for all patients admitted to the study hospital for treatment of AAWS (see Appendix 1 and 2 for Protocol forms). Patients were randomized to receive either a single dose of i.v. phenobarbital (10 mg/kg in 100 mL normal saline) or 100 mL normal saline, both delivered as clear solutions in same-sized, identical-appearing covered plastic bags, prepared by the pharmacy and infused over 30 min. The enrolling provider estimated patient weight. The study medication was requested from the pharmacy at the same time the alcohol withdrawal protocol was initiated. All study patients were placed on a cardiac monitor with continuous pulse oximetry while in the ED.

Methods of Measurement

Time of arrival in the ED, initial vital signs, initial Alcohol Withdrawal Clinical Assessment (AWCA) score, timing