Journal of Critical Care 32 (2016) 101–107

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Barbiturates for the treatment of alcohol withdrawal syndrome: A systematic review of clinical trials☆

Yoonsun Mo, MS, Pharm.D., BCPS, BCCCP [a,b,*], Michael C. Thomas, Pharm.D., BCPS, FCCP [a,1], George E. Karras Jr., MD, FCCM [b,2]

[a] Department of Pharmacy Practice, Western New England University College of Pharmacy, 1215 Wilbraham Road, Springfield, MA 01119
[b] Mercy Medical Center, 271 Carew Street, Springfield, MA 01104

ARTICLE INFO

Keywords:
Barbiturates
Phenobarbital
Benzodiazepines
Alcohol withdrawal syndrome
Delirium tremens
Systematic review

ABSTRACT

Purpose: To perform a systematic review of the clinical trials concerning the use of barbiturates for the treatment of acute alcohol withdrawal syndrome (AWS).
Materials and Methods: A literature search of MEDLINE, EMBASE, and the Cochrane Library, together with a manual citation review was conducted. We selected English-language clinical trials (controlled and observational studies) evaluating the efficacy and safety of barbiturates compared with benzodiazepine (BZD) therapy for the treatment of AWS in the acute care setting. Data extracted from the included trials were duration of delirium, number of seizures, length of intensive care unit and hospital stay, cumulated doses of barbiturates and BZDs, and respiratory or cardiac complications.
Results: Seven studies consisting of 4 prospective controlled and 3 retrospective trials were identified. Results from all the included studies suggest that barbiturates alone or in combination with BZDs are at least as effective as BZDs in the treatment of AWS. Furthermore, barbiturates appear to have acceptable tolerability and safety profiles, which were similar to those of BZDs in patients with AWS.
Conclusions: Although the evidence is limited, based on our findings, adding phenobarbital to a BZD-based regimen is a reasonable option, particularly in patients with BZD-refractory AWS.

1. Introduction

Approximately 15% to 20% of hospitalized patients and 50% of trauma patients suffer from alcohol use disorders [1,2]. Many of these patients manifest signs and symptoms of alcohol withdrawal syndrome (AWS) when their alcohol consumption is abruptly stopped or significantly reduced [3,4]. Patients with AWS exhibit a wide array of symptoms including tremor, tachycardia, nausea, insomnia, agitation, hallucination, diaphoresis, or tonic-clonic seizures [2,4]. Alcohol withdrawal delirium, also known as delirium tremens (DTs), is the most severe manifestation of AWS. It is characterized by a fluctuating mental state marked by disturbances of attention and awareness, disorientation, diminished responsiveness, hallucinations, or delusions combined with alcohol withdrawal symptoms [3,5]. About 5% of hospitalized patients with AWS will progress to DTs typically 48 to 72 hours after alcohol cessation [4,6]. The serious complications of AWS such as alcohol withdrawal delirium and seizures often lead to intensive care unit (ICU) admission, prolonged hospital and ICU stay and increased mortality ranging from 5 to 15% [4–7].

Benzodiazepines (BZDs) have been a mainstay of therapy for prevention and treatment of AWS [2,4,6,7]. However, there are limited data available on whether BZDs have definite superiority in managing AWS and its complications when compared with other agents [3]. In addition, some patients with severe AWS may not respond to high doses of BZDs, as they develop tolerance over time due to the γ-aminobutyric acid (GABA) receptor desensitization [4,6,8]. Benzodiazepine-refractory (or resistant) withdrawal symptoms may be described as uncontrolled agitated states despite of the need for >40 mg of lorazepam (LZP) in the first 3 to 4 hours, but it has not been well defined in the current literature [4,9]. Patients with BZD-refractory withdrawal symptoms are more likely to require continuous BZD infusion, which may result in a higher rate of mechanical ventilation and longer ICU and hospital stays [4,6].

Recently, there has been growing interest in the use of dexmedetomidine as adjunctive therapy to BZDs for the treatment of AWS. Dexmedetomidine, a presynaptic α_2-receptor agonist, could be an attractive option particularly in severe AWS patients experiencing respiratory depression from BZD therapy since it dose not cause respiratory depression [10]. Studies have suggested that dexmedetomidine as an adjunct in AWS may decrease alcohol withdrawal symptoms and benzodiazepine use, thereby potentially preventing mechanical ventilation [11,12]. However, it should be noted that clinical outcome data of

☆ Conflict of interest statement: All authors have no financial interest to declare in relation to the subject matter of this manuscript.

* Corresponding author. Tel.: +1 413 796 2443; fax: +1 413 706 2266.
E-mail addresses: yoonsun.mo@wne.edu (Y. Mo), michael.thomas@wne.edu (M.C. Thomas), George.Karras@sphs.com (G.E. Karras).
[1] Tel.: +1 413 796 2425.
[2] Tel.: +1 413 748 9860.

http://dx.doi.org/10.1016/j.jcrc.2015.11.022
0883-9441/

dexmedetomidine in AWS were very limited to a handful of case reports/series and observational studies and one small prospective controlled trial [10–14]. Additionally, dexmedetomidine therapy is more costly and resource-intensive than other alternatives. As a result, the clinical impact of dexmedetomidine in AWS still remains unclear.

Previous studies have demonstrated the use of barbiturates, GABA receptor agonists similar to BZDs, as an adjunctive to BZD therapy may be effective and safe in severe AWS refractory to BZD [15,16]. Of interest, in such patients, phenobarbital (PB) may play a role in reducing the need for ICU admission as well as mechanical ventilation [15–17]. Intravenous (IV) PB in particular has great potential in the treatment of severe AWS for the following reasons: (1) An IV formulation of PB can be especially useful when treating patients with acute AWS or DT compared to oral drugs, (2) IV PB can suppress acute withdrawal symptoms quickly due to its rapid onset of action (approximately 5 minutes) (3) Patients are less likely to require subsequent oral PB for AWS because PB concentrations gradually decline following iv injections due to its long duration of action (a half-life of 53-140 hours), and (4) From a safety standpoint, PB doses used for the treatment of hypnosedative withdrawal do not produce prominent central nervous system (CNS) depression [18–20]. Therefore, we conducted a systematic review of the current literature to assess the efficacy and safety of barbiturates with or without BZDs versus BZDs for the treatment of AWS in the acute setting. Additionally, the secondary objective was to evaluate the clinical utility and potential of PB in terms of preventing or reducing ICU admission as well as mechanical ventilation in patients developing acute AWS.

2. Materials and methods

2.1. Data sources

We developed a comprehensive list of keywords to identify all relevant studies for inclusion, which included alcohol withdrawal syndrome, alcoholism, alcohol dependence, delirium tremens, barbiturates, and benzodiazepine. A literature search was performed using MEDLINE (1946-July 2015), EMBASE (1947-July 2015), and the Cochrane Library (1992-July 2015). Additionally, a manual review of citations from retrieved articles was performed to capture relevant studies that are not indexed in the electronic bibliographic databases.

2.2. Study selection

Trials were included if they contained all of the following PICOTS (population, intervention, comparison, outcome, timing, and setting and study design) criteria: (1) Studies included inpatients with AWS; (2) Any barbiturates given as a single agent or with other agents were compared to BZDs alone or BZDs in combination with other agents; and (3) Randomized controlled trials, non-randomized controlled trials, and observational studies with comparison groups were included in the final analysis. All other types of clinical trials including case reports and series were excluded. Primary outcomes were total cumulative doses of barbiturates and BZD, duration of delirium, number of seizure episodes, or respiratory and cardiovascular complications. Secondary outcomes included length of ICU and hospital stay.

2.3. Data extraction and synthesis

Two authors (YM, MT) and one professional librarian (EL) independently screened and selected studies for inclusion. Discrepancies were resolved through discussions and consensus. We chose the Mixed Methods Appraisal Tool (MMAT) to evaluate the methodological quality of each study due to the nature of studies included in this review, mixed methods studies [21]. Two independent reviewers (YM, MT) assessed the quality of evidence using the MMAT scoring metrics. An overall quality score for each study was assigned based on the number of criteria met, ranging from 25% (*) to 100% (****). In case of disagreement between the two reviewers, we sought a second opinion from an external person with expertise in drug information/informatics before making the final assessment decision.

3. Results

Our initial screen of titles and abstracts resulted in a total of 98 studies, out of which 29 citations possibly eligible by inspection of abstracts were retrieved for full-text review (Figure). Ultimately, eight articles were retained for final inclusion; however, following the quality appraisal process, one study was excluded from our systematic review due to its small and unbalanced sample size between groups (pre-guideline group, n = 30 vs post-guideline group, n = 3) [22]. A summary of included clinical trials is depicted in Table.

3.1. Randomized controlled trials (RCTs)

In our analysis, we identified three RCTs, including two double-blind trials and one partially double-blind study [16,23,24]. Rosenson and colleagues published a double-blind, randomized, placebo-controlled trial of PB for the treatment of acute alcohol withdrawal in the emergency department (ED) [16]. A total of 102 patients with a primary admission diagnosis of acute AWS were randomly assigned to receive either a single dose of intravenous (IV) PB (10 mg/kg, n = 51) or placebo (n = 51). In addition to study drugs, all patients were placed on a symptom-triggered LZP protocol for AWS. Baseline characteristics including initial median alcohol withdrawal clinical assessment (AWCA) scores (6 PB vs 7 placebo [mild-moderate withdrawal if AWCA score were between 3 and 10]) were similar in both groups. The authors observed significant decreases in ICU admission rate (8% vs 25%, difference 17% [95% confidence interval (CI) 4-32%]) and use of continuous LZP infusion (4% vs 31%, difference 27% [95% CI 14%-41%]) in PB group as compared with placebo group. Furthermore, there were no significant differences in adverse effects including the requirement for intubation or restraints and seizure between the two groups. However, it needs to be acknowledged that decisions on ICU admission and initiation of continuous LZP drip were made solely at the discretion of ED providers.

Results from two other studies demonstrated favorable outcomes of barbiturates in the treatment of AWS, but failed to show superiority of barbiturates over BZDs, especially in regards to controlling alcohol withdrawal (AW) symptoms [23,24]. Of note, these studies compared barbiturates alone with other agents. Kaim and colleagues conducted a randomized, partially double-blind trial to evaluate the effectiveness of sodium pentobarbital, chlordiazepoxide, paraldehyde, and perphenazine for the treatment of uncomplicated DTs [23]. Patients in the three groups (pentobarbital, n = 46; chlordiazepoxide, n = 46; perphenazine, n = 46) initially received intramuscular (IM) injections in a double-blind fashion followed by oral capsules identical in appearance, whereas those in the paraldehyde group (n = 55) were treated with a liquid oral formulation. The authors did not find any significant differences in the duration ($P > .2$) or severity ($P > .1$) of AW symptoms among the 4 groups. One of the major drawbacks of this study is that investigators solely relied on the subjective clinical assessments to measure study outcomes.

In Hendey's study, patients in the ED with acute AW were randomized into two groups: 25 patients were treated with IV PB (a 260-mg dose followed by subsequent doses of 130 mg) and 19 patients received IV LZP (2 mg). In both groups, the timing and number of subsequent doses were up to the treating physicians [24]. This study found no differences in AW symptom control, ED length of stay, hospital admission rates, or 48-hour follow-up Clinical Institute Withdrawal Assessment (CIWA) scores between the two groups. The authors concluded that PB and LZP were similarly effective in ED patients with acute AWS. However, 48-hour follow-up results should be interpreted with caution because only 40% (18/44) patients returned for 48-hour follow-up