


Thiamine Dosing for the Treatment of Alcohol-Induced Wernicke's Encephalopathy: A Review of the Literature

Journal of Pharmacy Technology
2021, Vol. 37(2) 107–113
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DOI: 10.1177/8755122520962859
journals.sagepub.com/home/pmt


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Abstract

Objective: To determine the most appropriate thiamine replacement regimen by evaluating safety and efficacy of the drug specific to alcohol-induced Wernicke's encephalopathy (WE). **Data Sources:** A comprehensive literature search was conducted using PubMed, MEDLINE, Scopus, and ProQuest between January and August 2020 using the following keyword and Boolean search terminology: "thiamine" AND "alcohol" AND (encephalopathy OR korsakoff). **Study Selection and Data Extraction:** Randomized control trials; prospective, observational, and retrospective cohort analyses; and case reports and series were included in this evaluation. A confirmed diagnosis of alcohol-induced WE and treatment with parenteral or intramuscular (IM) thiamine were required for inclusion. **Data Synthesis:** Six publications composed of 138 patients were evaluated in this review, in which a wide variety of thiamine supplementation strategies were employed. Clinical diagnostic criteria varied significantly between publications. Doses ranged from 100 to 1500 mg intravenous thiamine and up to 300 mg IM thiamine, with no apparent difference in patient outcomes. All patients who received thiamine experienced symptom improvement, and adverse drug events were minimal. **Conclusions:** Despite the clinical controversy regarding the appropriate thiamine supplementation regimen, the heterogeneity of published works combined with symptom resolution across the gamut of dosing strategies makes a definitive consensus elusive. Clinicians should continue to provide parenteral or IM thiamine in doses of ≥ 100 mg to patients with confirmed alcohol-induced WE.

Keywords

alcohol intoxication, substance abuse, evidence-based medicine, clinical pharmacy, clinical toxicology

Introduction

Wernicke's encephalopathy (WE) can be a result of alcohol-induced thiamine deficiency and is a common manifestation of those who suffer from alcohol use disorder (AUD).¹ AUD is defined as a brain disease distinguished by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using alcohol.¹ According to the Substance Abuse and Mental Health Services Administration, which conducts the annual National Survey on Drug Use and Health, in 2018, 6.6% of people aged 18 years or older stated that in the past month, they engaged in heavy alcohol use.² The Centers for Disease Control and Prevention reported that from 2006 to 2010, an estimate of 88000 people died in the United States due to alcohol-related causes.³ The number of visits to US emergency departments due to alcohol abuse has increased by 50% between the years of 2006 and 2014, according to the National Institute on Alcohol Abuse and Alcoholism.⁴ Alcohol can negatively influence various aspects of one's

health, whether it be physically or mentally. Chronic alcohol use can result in cardiovascular issues (ie, cardiomyopathy, arrhythmias, stroke, and high blood pressure), hepatic insufficiency (ie, steatosis, alcoholic hepatitis, fibrosis, and cirrhosis), pancreatitis, various types of cancers, and can also weaken the immune system.⁵ In addition, chronic alcoholism has been associated with motor vehicle accidents, violence, mental health issues, and unemployment.^{6,7} Alcohol abuse is furthermore commonly associated with thiamine deficiency that can further manifest as WE.⁸

The classic triad of clinical manifestations associated with WE includes confusion, ataxia, and ophthalmoplegia.⁸ If the disease continues to progress, Korsakoff syndrome

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PubMed and MEDLINE

thiamine AND alcohol AND (encephalopathy OR korsakoff)

Specifiers: "Language: English"; "Species: Human"; "Article type: case reports, clinical conference, clinical study, clinical trial, clinical trial phase I, clinical trial phase II, clinical trial phase III, clinical trial phase IV"

Sort by: Best Match

Scopus

thiamine AND alcohol AND (encephalopathy OR korsakoff)

Specifiers: "Document type: articles"; "Language: English"; "Source type: Journals"; "Exact keyword: Human"

ProQuest

thiamine AND alcohol AND (encephalopathy OR korsakoff)

Specifiers: "Document type: article, features, report, and case studies"; "Language: English"

Figure 1. Search criteria.

can occur, presenting with chronic cognitive impairment seen as severe memory loss and learning deficits deeming it a medical emergency.^{9,10} In most cases, those with WE will not experience the entire triad of symptoms, therefore making the diagnosis somewhat challenging and also the classic triad an unreliable tool for diagnosis.¹¹ In WE, the brain undergoes high metabolic demands due to the depletion of thiamine stores.¹² The brain experiences oxidative stress and lactic acidosis, and inflammation is also present, leading to the disruption of the blood-brain barrier and alterations in the function of the neurologic system.¹² The current treatment for WE, although not consistently approached, includes intravenous (IV) or intramuscular (IM) administration of thiamine followed by a glucose infusion.⁸

Thiamine, also referred to as vitamin B₁, is 1 of the 12 water-soluble vitamins, and it plays a significant role in the maintenance of the nervous system.¹³ Thiamine also plays a key role in the metabolism of glucose and, therefore, energy production.¹⁴ Alcohol consumption alone reduces intestinal absorption of thiamine, rendering oral administration of thiamine insufficient for the treatment of WE.¹⁵ As is evident from primary literature and case reports, the administration of oral thiamine alone was insufficient in adequately addressing WE symptoms.^{16,17} In a case report presented by Chataway and Hardman, a patient was started on 200 mg of PO thiamine for 12 days. Ten weeks later, the patient was readmitted with a diagnosis of WE and 400 mg of oral thiamine was initiated.¹⁶ The patient did experience gradual symptomatic improvement, but was left with residual fine lateral nystagmus.¹⁶ Another case report by Yoon et al presented a 56-year-old male who had a remarkable past medical history that included AUD. This patient also received strictly oral thiamine supplementation at a dose of 200 mg daily.¹⁷ Cognition and balance gradually improved, but the patient was found to have a left-beating horizontal nystagmus halfway through his admission.¹⁷ In both of these case reports, findings showed that oral thiamine was not adequate enough to completely stabilize the patient and reverse their symptoms. The transport of oral thiamine across the

blood-brain barrier through various mechanisms has been shown to be a slower process when compared with parenteral administration.¹⁵ Parenteral thiamine is capable of rapid correction of depleted stores and provides therapeutic plasma levels that assist in reversal of the patient's neurologic symptoms.¹⁵ As for the acute management of WE, it is recommended that IV supplementation, rather than oral supplementation, be provided. For the treatment of WE, the package insert for thiamine recommends administering 100 mg of thiamine intravenously followed by IM doses of 50 to 100 mg until the patient is able to return to a regular diet.¹⁸ However, there is not a clear consensus or high-quality evidence that supports this recommendation. Both the British Association of Psychopharmacotherapy and the Royal College of Physicians guidelines recommend that confirmed cases of WE should be treated with parenteral doses of thiamine greater than 500 mg per day for at least 3 to 5 days.^{15,19} In addition, magnesium supplementation should occur if hypomagnesemia is present as it functions as a cofactor for the conversion of thiamine.^{15,20} The objective of this literature review was to evaluate effective dosing regimens of thiamine supplementation in WE.

Methods

A comprehensive literature review was conducted by all 4 authors, with assistance from a medical reference librarian, utilizing PubMed, MEDLINE, Scopus, and ProQuest between January and August 2020. Search identifiers were then added to further enhance the relevance of the articles that were pertinent to this review. The search criteria within each database is further described in Figure 1. After assessing whether articles met inclusion and exclusion criteria, the search was narrowed down to 6 articles that were relevant; this process is depicted in Figure 2. Articles were included if participants had a diagnosis of alcohol-induced WE, outcome measures were documented, and if their treatment regimen included parenteral or IM thiamine of doses greater than or equal to 100 mg. Tertiary literature was

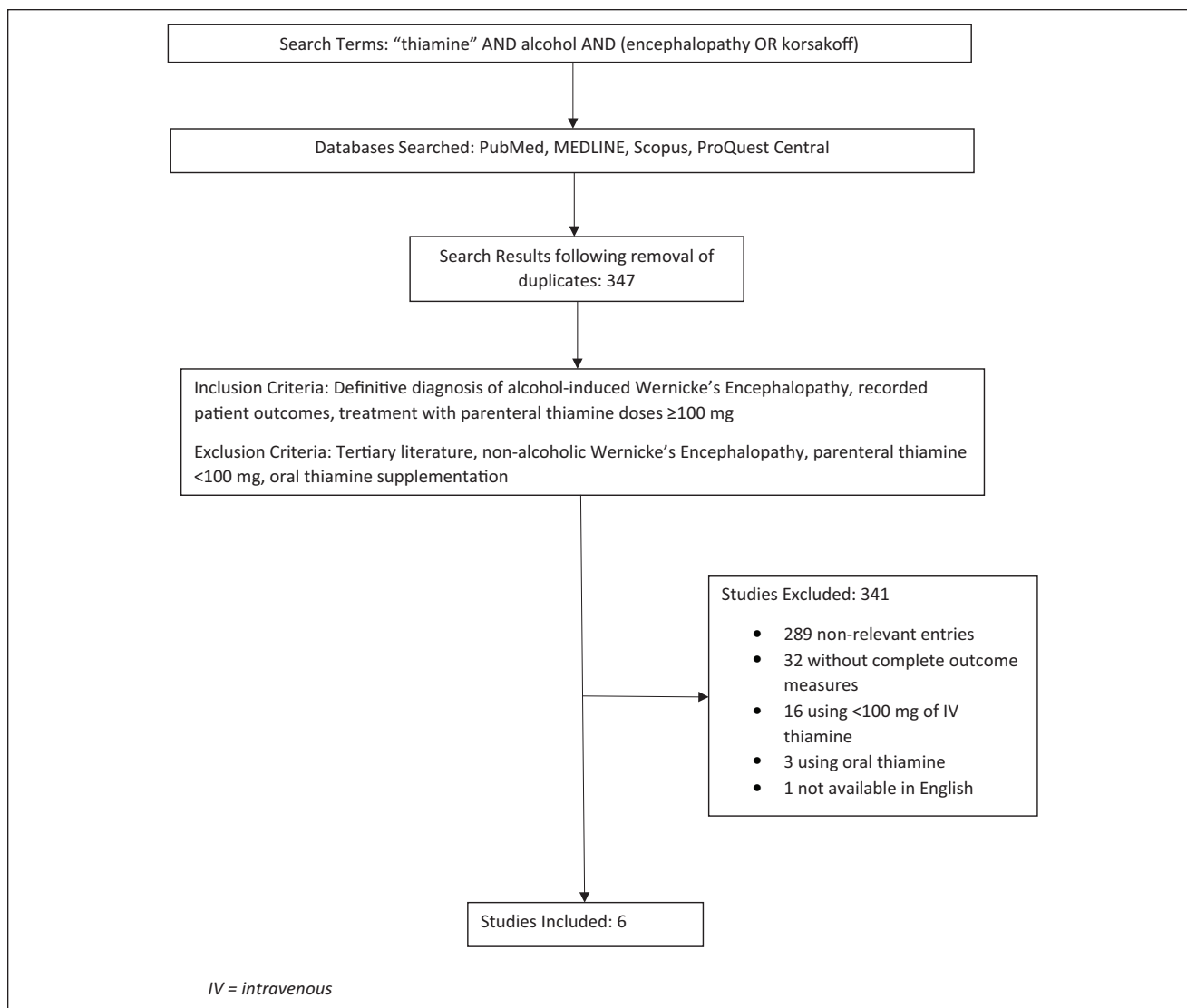


Figure 2. Schematic of search methodology. IV, intravenous.

excluded. Articles were also excluded if they evaluated participants with nonalcoholic WE, if the dose of thiamine was less than 100 mg, or if the participants only received oral thiamine supplementation.

Results

A total of 6 studies were included in this review, the details of which can be viewed in Table 1. Regarding the route of administration of thiamine, only 2 of the studies utilized both oral and parenteral routes.^{13,21} Each of the studies that were included in this review of literature confirmed that prompt administration of thiamine had an impact on improving symptoms associated with WE. In the 3 studies that had a sample size greater than 1, the onset of resolution of symptoms with higher doses of thiamine compared with

lower doses was inconclusive. The duration of therapy and the time to resolution of symptoms for each study varied, demonstrating no correlation between the 2 variables.

A case report by Paparrigopoulos et al presented a 52-year-old male who had a 10-year history of alcohol abuse.²¹ He was admitted for symptoms of WE and initially received 100 mg of thiamine intramuscularly daily.²¹ He was then given aggressive treatment with thiamine 600 mg/day orally and 300 mg/day intramuscularly.²¹ The patient's symptoms began improving within 3 weeks, and after a yearly checkup, the patient was reported to be functioning normally.²¹ The article recommended that higher doses should be utilized for a longer duration, for most treatment regimens are subtherapeutic due to the fact that treatment must be initiated immediately to prevent irreversible damage.²¹

Table 1. Results.

Study	Study design	Number of participants	Thiamine regimen	Duration of thiamine supplementation	Diagnosis criteria utilized	Effect/primary outcome	Comments
Paparrigopoulos et al ²¹	Case report	1	600 mg PO daily and 300 mg IM daily	2 months	MMSE	Complete resolution of symptoms	Resolution occurred following 2 months of treatment with this regimen
Pandey et al ²²	Case report	1	500 mg IV	1 day	Clinical presentation; MRI findings	Improvement of symptoms	Utility of a single dose of thiamine demonstrated
Tjong and Peng ²³	Case report	1	500 mg IV followed by 1000 mg IV	5 days	Caine's criteria	Complete resolution of symptoms	Concomitant diagnosis of beriberi in addition to WE
Nishimoto et al ¹³	Case series	11	<ol style="list-style-type: none"> 100 mg PO daily, 500 mg IV daily 100 mg PO, 500 mg IV q8hr, 500 mg IV qday, 100 mg PO daily 100 mg PO, 500 mg IV q8hr, 500 mg IV daily 100 mg PO, 500 mg IV BID, 500 mg IV daily 500 mg IV once, 100 mg PO daily 100 mg PO, 500 mg IV q8hr 500 mg IV q8hr, 200 mg IV daily, 100 mg PO daily 500 mg IV q8hr, 100 mg IV daily 500 mg IV q8hr, 100 mg PO daily 500 mg IV TID, 250 mg IV daily 500 mg IV TID, 500 mg IV daily 	<ol style="list-style-type: none"> 3 days 7 days 7 days 8 days 1 day 2 days 3 days 2 days 7 days 3 days 3 days 	<p>Clinical presentation and MRI findings</p> <p>Complete resolution of symptoms observed in 7/11 patients</p>	<p>Each patient (numbered 1-11) received a different thiamine regimen, some of which included initial oral supplementation. Patients who experienced symptom resolution received at least 3e days of thiamine supplementation as opposed to 2 or fewer days.</p>	
Alim et al ²⁴	Retrospective cohort	17	<p>High dose (n = 12): > 100 mg IV (highest dose was 1000 mg)</p> <p>Low dose (n = 5): < 100 mg IV</p>	<p>High doses: 6 to 8 days</p> <p>Low doses: 3 to 5 days</p>	Clinical presentation	Complete resolution of symptoms	<p>Nonsignificant decrease in time to resolution of symptoms of approximately 0.5 days appreciated between high- and low-dose cohorts.</p> <p>Median dose administered in the high-dose cohort was 400 mg IV. Sixty-five percent of doses were administered daily, while the remaining 35% were administered every 8 hours.</p>
Ambrose et al ²⁵	RCT, double blinded	107	<ol style="list-style-type: none"> 5 mg IM daily 20 mg IM daily 50 mg IM daily 100 mg IM daily 200 mg IM daily 	2 days	MMSE	Complete resolution of symptoms demonstrated in all patients; quicker resolution demonstrated for patients in the 100 and 200 mg IM cohorts	<p>The 107 participants were divided into 5 different groups to receive varying thiamine regimens. MMSE examination results were used as a surrogate for formal WE diagnosis. Baseline years of drinking was approximately 17.5, and the mean amount of alcohol consumed was approximately 300 g every 24 hours. Patients in the 200 mg IM cohort performed better on delay alternation tests than those in the 50 mg IM cohort.</p>

Abbreviations: PO, by mouth; IM, intramuscularly; MMSE, Mini Mental Status Examination; IV, intravenously; MRI, magnetic resonance imaging; WE, Wernicke's encephalopathy; q8hr, every 8 hours; BID, twice a day; TID, 3 times a day; RCT, randomized control trial.

Pandey et al reported a 45-year-old female who had a history of alcohol abuse who presented after 4 days of nausea, vomiting, dizziness, and falls.²² She displayed impaired cognition, appeared disoriented, slightly pale, and was foul smelling; there was no mention of other comorbidities.²² The patient was given 500 mg of IV thiamine, and afterward, the patient's symptoms dramatically improved.²²

Another case report by Tjong and Peng presented a 30-year-old male who had predisposed beriberi and developed WE 2 months after a single heavy drinking session, which resulted in a neurologic emergency deeming prompt treatment.²³ The patient was clearly malnourished, due to his inability to tolerate solid foods and the previous diagnosis of beriberi.²³ The patient was given 500 mg of IV thiamine and did not respond appropriately; another 500 mg was given.²³ It took 10 times the recommended dose to achieve clinical resolution, in which all neurologic symptoms were reversed within hours.²³

A case series by Nishimoto et al reported that of the 11 patients who were admitted with possible WE, all were treated with doses of thiamine >500 mg per day.¹³ Patients were enrolled in the case series through International Classification of Diseases, Ninth Revision (ICD-9) review.⁹ There was no mention of additional comorbid states amid the study population, although this information could have been useful. All the cases were treated with different protocols of dosing; some of the individuals were given oral thiamine first followed by parenteral treatment of 500 mg while others were started on parenteral treatment immediately.⁹ The majority of the cases had different time to resolution of symptoms based on the duration of high-dose thiamine given; there were some cases that were refractory to the thiamine treatment.⁹

A retrospective cohort conducted by Alim et al included both low-dose (defined as doses <100 mg) and high-dose (defined as doses >100 mg) IV thiamine prescribing patterns.²⁴ Of the 141 patients, only 17 of them were prescribed thiamine due to suspicion of WE.²⁴ For those suspected to have WE, 12 patients received high-dose thiamine.²⁴ Other comorbidities that were reported among the study population included the following types of liver dysfunction: cirrhosis, nonalcoholic fatty liver disease, alcoholic hepatic steatosis, hepatocellular carcinoma, alcoholic hepatitis, and viral hepatitis.²⁴ The study revealed that of the 141 patients receiving either high-dose or low-dose thiamine, no patient showed significant differences in time of resolution of the triad of symptoms.²⁴ For confusion, ataxia, and ocular abnormalities, 13 participants, 6 participants, and 7 participants in the high-dose groups experienced resolution of symptoms, respectively.²⁴

A randomized control trial by Ambrose et al was conducted in which 107 participants who were detoxifying from alcohol were split into 5 different groups to receive varying doses of parenteral thiamine treatment.²⁵ The groups received the following daily doses of IM thiamine

for 2 consecutive days: 5 mg, 20 mg, 50 mg, 100 mg, and 200 mg.²⁵ Each subject had an average of 17 years of alcohol consumption, but there was no mention of confounding disease states among any of the patients.²⁵ Each of the groups performed similarly on the Mini Mental Status Examination (MMSE) at baseline, indicating that there was no significant difference in the mental cognition of each participant.²⁵ The results of this trial concluded that increased doses corresponded with higher working memory performances as quantified by the delayed alternation method, a test conducted by a psychologist to determine the delay in responses to verbal stimuli.²⁵

Discussion

Results from the selected literature demonstrated the efficacy of thiamine doses greater than or equal to 100 mg, in alignment with the product package insert, both intravenously and intramuscularly at various dosing intervals in the treatment of alcohol-induced WE.¹⁸ Due to the similar responses seen with the varying thiamine regimens among each study, it is imperative that treatment of alcohol-induced WE be patient specific, with a dose and duration of thiamine sufficient to mitigate the patients' symptoms. Factors that affect dosing decisions are numerous, but may include the duration of alcohol exposure, the time since last alcoholic beverage consumption, the presence of malnutrition markers including hyponatremia, the rapidity of onset of WE, and severity of present symptoms.

As is the case in clinical practice, numerous different dosing regimens are described in the results of this review. While all trials reported efficacy of thiamine \geq 100 mg administered in a route other than orally, perhaps the most poignant argument for administering high doses of thiamine can be derived from Ambrose et al.²⁵ The 5 dosing regimens employed in this trial ranged from 5 mg to 200 mg IM thiamine administered daily, and the patients who received the highest doses experienced the most rapid resolution of symptoms and demonstrated higher mental acuity.²⁵ This trend aligns with other subsequently conducted evaluations included in this review, in that patients who received high doses of thiamine experienced a shorter duration of symptoms associated with WE.^{21-23,25}

While the assessment of doses and routes of administration of supplemental thiamine deserves significant attention, perhaps equally important is the duration of therapy. In the trial conducted by Nishimoto et al, 4 of 11 patients did not experience a resolution of symptoms despite receiving high-dose thiamine, defined by the authors as >500 mg IV daily.¹³ In a review of the patients whose symptoms resolves in comparison to those whose did not, the duration of therapy becomes significant: patients who experienced symptoms resolution were treated with the high-dose thiamine regimen for 3 days, as opposed to being administered

Table 2. Caine Criteria.²⁶

Requires 2 of the following 4 for a diagnosis of WE:

1. Dietary deficiencies
2. Oculomotor abnormalities
3. Cerebral dysfunction
4. Either an altered mental state or mild memory impairment

Abbreviation: WE, Wernicke's encephalopathy.

Table 3. Recommended Thiamine Protocol for Alcohol-Induced Wernicke's Encephalopathy.^{15,19,20}

Dose and frequency	Route	Duration
Thiamine 500 mg every 8 hours PLUS Magnesium sulfate 35-50 mmol, if hypomagnesemia is present	Intravenous	Minimum of 3 days

for 2 days in the patients who did not experience a resolution of symptoms.¹³ While the patient evaluated by Pandey et al experienced improvement in symptoms after a single 500 mg IV dose of thiamine, it may be reasonable to consider a minimum of 72 hours of treatment with a high-dose thiamine strategy to achieve a complete resolution of symptoms.^{13,22}

Visual assessment of patients in conjunction with a thorough physical examination are important in the diagnosis of WE; however, the symptoms associated with this syndrome may mimic other pathologies, making a definitive diagnosis difficult. In an effort to elucidate WE-specific symptomatology, the Caine criteria were developed, though based on the results of this review, are only sporadically employed.^{22,23} The Caine criteria can be viewed in Table 2²⁶. Three of the 6 studies that we analyzed did not specify an objective method of assessing symptom improvement, and relied on clinical observational reports. Though unvalidated for this indication, the MMSE was utilized in 2 of the studies as a means of assessing treatment efficacy and the diagnosis of WE.^{21,25}

Alcohol-induced WE is commonly underdiagnosed due to the nonspecific patient presentation, which makes the evaluation in the clinical trial setting difficult. Additionally, specific treatment regimens are not well defined within the literature, as is evidenced in the wide variety of options contained within this review. Although there was a resolution of symptoms seen with lower doses of thiamine, the heterogeneity among the selected studies makes it difficult to identify a conclusive dose of thiamine supplementation. Based on the outcomes of the data collected throughout our literature search and both the British Association of Psychopharmacotherapy and the Royal College of Physicians guidelines, in conjunction with the results of this review, a reasonable strategy would be the regimen presented in Table 3.^{15,19} Because of current knowledge on bioavailability and increased absorption via the parenteral

route in patients who present with alcoholic WE, oral supplementation should not be considered in this patient population. Additionally, magnesium supplementation along with thiamine should be considered because magnesium is a cofactor for the transketolase and pyruvate decarboxylase reactions, and is important for the conversion of thiamine into its active form.^{15,20}

Several limitations exist that warrant discussion. As with any review of the literature, the search methodology or criteria may have inadvertently excluded articles that may have been of benefit to this report. The overall paucity of randomized clinical trials for the evaluation of thiamine dosing for the management of WE severely diminishes the external validity and generalizability of our findings, especially those derived from case reports and case series. The heterogeneity of trial design, dosing regimens, routes of administration of thiamine, and outcome measures similarly add difficulty in making a definitive consensus on an appropriate thiamine regimen for the treatment of alcohol-induced WE. As the largest comprehensive health organization that provides specific recommendations for the treatment of alcohol-induced WE, the Royal College of Physicians guidelines should be utilized until further conclusive research has been conducted.

Conclusions

Inconclusive data exist with regard to a specific thiamine dosing regimen for the treatment of alcohol-induced WE. Based on the information available from clinical trials, it may be reasonable to treat patients with a high-dose thiamine regimen including 500 mg IV thiamine every 8 hours for at least 3 days, in addition to the supplementation of magnesium if appropriate given patient serum levels. Further clinical investigations are warranted in which the diagnosis of WE, and the dosing and duration of thiamine supplementation is consistently defined among all study participants.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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