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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Which patients hospitalized with alcohol withdrawal syndrome should receive high-dose parenteral thiamine?

A: All patients hospitalized with alcohol withdrawal syndrome who have severe or complicated withdrawal (eg, severe symptoms, hallucinations, seizures, or withdrawal delirium) and evidence of malnutrition or malabsorption and patients admitted to the intensive care unit to treat alcohol withdrawal should receive high-dose parenteral thiamine to treat Wernicke encephalopathy.[1,2]

We suggest using clinical criteria to risk-stratify all other patients hospitalized with alcohol withdrawal syndrome for Wernicke encephalopathy, as high-risk patients warrant treatment regardless of severity of withdrawal. Pharmacokinetic data indicate that currently available oral thiamine formulations are absorbed too slowly to replenish depleted brain stores, and parenteral thiamine administration is required.[3] There is no consensus on the optimal dose and duration of parenteral thiamine, but its short half-life and water solubility suggest that divided dosing (2 or 3 times daily) would lead to better tissue repletion than once-daily dosing.[3–6]

WERNICKE ENCEPHALOPATHY: UNDERDIAGNOSED AND UNDERTREATED

Wernicke encephalopathy is an acute neurocognitive syndrome caused by depletion of intracellular stores of thiamine (also known as vitamin B_1), an enzymatic cofactor essential in carbohydrate metabolism.[4] Patients with alcohol use disorder, with or without malnutrition, are at increased risk for Wernicke encephalopathy, which autopsy studies suggest is underdiagnosed.[1] Due to nonspecific symptoms and other causes of encephalopathy (including infection, withdrawal delirium, and hepatic encephalopathy) in high-risk patients, it is estimated that only 5% of cases of Wernicke encephalopathy found on autopsy are diagnosed antemortem.[1] Untreated, Wernicke encephalopathy is fatal in up to 20% of patients, and progression to Korsakoff syndrome, a devastating anterograde and retrograde amnesia, occurs in more than half of survivors, many of whom require long-term institutional care.[1,3,4,7] If treated early, the neuropsychiatric abnormalities of Wernicke encephalopathy are often reversible,[2,4] highlighting the importance of promptly identifying high-risk patients.

Clinical manifestations include confusion, oculomotor abnormalities, and gait disturbances; hypothermia and hypotension may also occur.[1] The classic triad of encephalopathy, nystagmus, and ataxia occurs only rarely and late in the disease course, and there are no reliable laboratory or imaging criteria to establish the diagnosis of Wernicke encephalopathy.[4] Serum thiamine levels correlate poorly with tissue stores, and test results may not be available for several days. For these reasons and owing to the urgency of treatment, laboratory measurement is of limited value and is not routinely recommended to guide treatment decisions.

WHICH PATIENTS SHOULD ALWAYS BE TREATED?

Given the challenge in accurately diagnosing Wernicke encephalopathy, the American Society of

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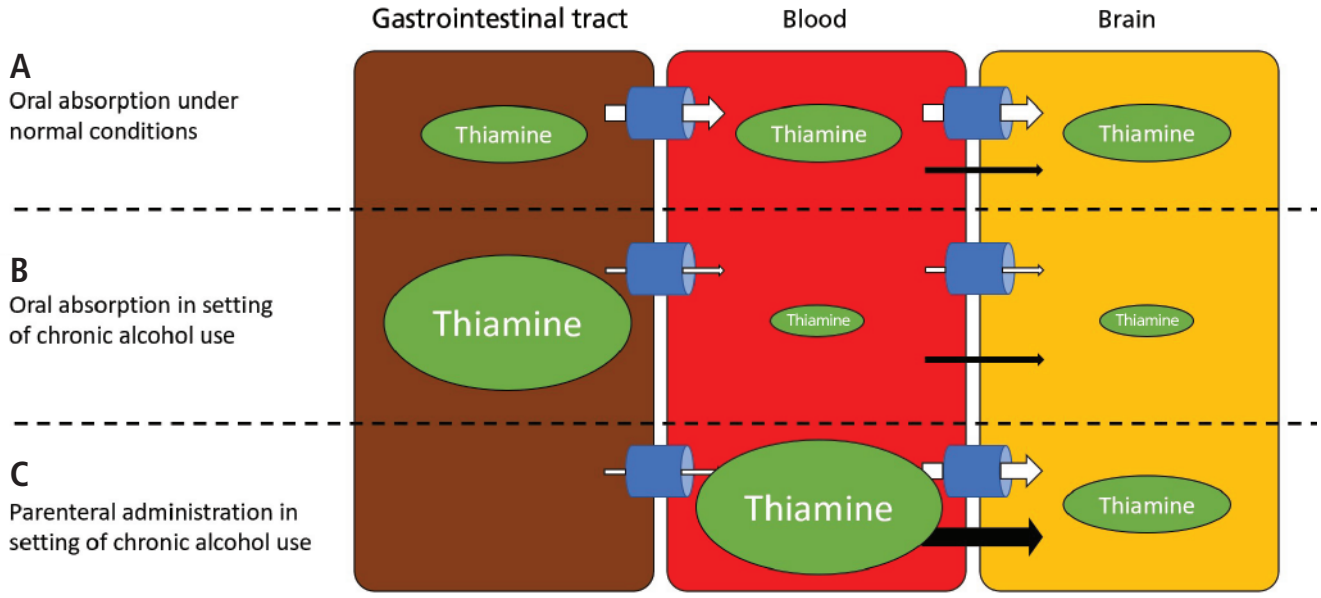

Figure 1. The three compartments above represent the gastrointestinal tract lumen on the left, the blood in the middle, and the brain on the right. The size of the green ovals is proportional to the concentrations of thiamine in each compartment, and the width of the arrows is proportional to the amount of uptake by each mechanism. The three rows diagram a schematic representation of (A) oral thiamine absorption under normal conditions, (B) oral thiamine absorption in the setting of chronic alcohol use, and (C) parenteral thiamine administration in the setting of chronic alcohol use. Under normal conditions, most uptake from the gastrointestinal tract to the blood and from the blood to the brain occurs via a membrane-bound transporter (white arrows) and little occurs via passive diffusion (black arrows). The relative proportions are altered in chronic alcohol use and with the administration of parenteral thiamine.

Addiction Medicine's 2020 guidelines recommend parenteral thiamine administration in patients hospitalized for alcohol withdrawal syndrome and any of the following[2]:

- Symptoms of severe or complicated withdrawal
- Evidence of malnutrition
- Evidence of malabsorption
- Admission to the intensive care unit to treat alcohol withdrawal syndrome.

This recommendation will result in some patients without thiamine deficiency receiving high-dose parenteral treatment. However, considering the availability, low cost, and safety of parenteral thiamine, empiric administration is recommended in high-risk populations to avert the dire consequences of untreated Wernicke encephalopathy.[2]

WHICH PATIENTS SHOULD BE RISK-STRATIFIED?

All patients admitted with alcohol withdrawal syndrome are at high risk for thiamine deficiency and should be risk-stratified for Wernicke encephalopathy because high-dose parenteral thiamine is warranted in all high-risk patients.[2] In a 1997 paper, Caine et al[8] compared autopsy findings with neurologic and neuropsychological assessments from 106 patients with alcohol use disorder to develop and validate operational criteria for the diagnosis of Wernicke encephalopathy in patients with alcohol use disorder. We favor this approach to risk stratification owing to the high sensitivity of history and physical examination findings alone. Any 2 of the following 4 criteria had sensitivity of 100% for predicting diagnosis of Wernicke encephalopathy[8]:

- Dietary deficiencies (body mass index ≥ 2 standard deviations below normal, history of grossly impaired oral intake, or low serum thiamine level)
- Oculomotor abnormalities (ophthalmoplegia, nystagmus, or gaze palsy)
- Cerebellar dysfunction (ataxia, unsteadiness, dysmetria, dysdiadochokinesia, or impaired heel-shin testing)

- Altered mental state or mild memory impairment (disorientation in 2 of 3 fields, confusion, abnormal digit span, or coma).

THIAMINE TREATMENT: ROUTE, DOSING, AND DURATION

Chronic alcohol use, with or without malnutrition, reduces intestinal thiamine absorption by up to 50%, severely limiting the ability of even large oral doses to correct tissue deficiencies (**Figure 1A and 1B**).[4] In the setting of chronic alcohol use, parenteral administration of thiamine offers 2 benefits: it overcomes reduced gastrointestinal absorption and creates a large concentration gradient between the blood and brain that drives an increase in the passive diffusion of thiamine across the blood-brain barrier, allowing replenishment of depleted stores (**Figure 1C**).[4] These observations support the administration of parenteral thiamine to treat Wernicke encephalopathy. When comparing intravenous and intramuscular administration, our practice is to administer intravenous thiamine when feasible, with intramuscular administration as an acceptable alternative.

There is no consensus on the optimal dose or duration of parenteral thiamine required to treat Wernicke encephalopathy. In their 2020 guidelines, the American Society of Addiction Medicine cites 100 mg/day intravenously or intramuscularly for 3 to 5 days as typical dosing in the absence of data from high-quality randomized controlled trials.[2] In addition, small studies done in the 1980s and 1990s suggest that parenteral doses below 250 mg daily may not consistently reverse signs and symptoms of Wernicke encephalopathy.[3] This concern has led some to recommend higher doses up to 500 mg 2 or 3 times daily, without strong evidence.[3,4,5,7] A recent single-center randomized controlled trial comparing different dosages of parenteral thiamine found no evidence of an effect of dose on neurologic and cognitive outcomes in patients at risk for Wernicke encephalopathy; however, this study was limited by small sample size, high attrition, and short duration of follow-up.[6] Fortunately, adverse effects from parenteral thiamine administration are uncommon. Although early case reports of anaphylaxis from rapid administration of intravenous thiamine have raised concern, the risk is now believed to be exceedingly rare, especially when thiamine is administered over 30 minutes.[4]

In the absence of data from high-quality dose-ranging studies, pharmacokinetic principles can inform dosing decisions. Because thiamine is a water-soluble vitamin with an elimination half-life of only 96 minutes, it is rapidly cleared from the system.[5] Given the importance of a large concentration gradient to drive passive diffusion across the blood-brain barrier, parenteral administration in divided doses (2 or 3 times daily) provides more opportunities to replenish tissue stores than once-daily dosing.

Clinical response to high-dose parenteral thiamine in patients with Wernicke encephalopathy is often brisk.[1] Once treatment is initiated, oculomotor abnormalities, if present, typically resolve the fastest, with improvement often evident within days.[1] Encephalopathy and ataxia take longer to improve, and gait impairment may persist as a lasting sequela.[1]

ORAL THIAMINE AT DISCHARGE

Unfortunately, high-quality evidence is lacking to inform which patients hospitalized with alcohol withdrawal syndrome should receive oral thiamine or multivitamin supplementation at hospital discharge.[9] Reflecting this uncertainty, current professional society guidelines do not offer definitive recommendations for prescribing oral thiamine at discharge for patients hospitalized with alcohol withdrawal syndrome.[2] We suggest engaging in shared decision-making to incorporate patient preferences and limit polypharmacy in determining who should receive oral thiamine supplementation at discharge.

THE BOTTOM LINE

Wernicke encephalopathy remains an underdiagnosed, undertreated, and potentially fatal and disabling complication of alcohol use disorder. Prompt recognition and treatment of Wernicke encephalopathy is an essential component of the care of patients hospitalized with alcohol withdrawal syndrome.[2,4] In the absence of high-quality evidence from randomized controlled trials, recommendations for thiamine administration and dosing are based on expert consensus and pharmacologic principles.[1,5,7] In the setting of chronic alcohol use with or without malnutrition, our practice is to administer intravenous thiamine in divided doses (2 or 3 times daily) for up to 5 days to ensure adequate replenishment of brain stores in all patients hospitalized with alcohol withdrawal syndrome who are high-risk for Wernicke encephalopathy. ■

Acknowledgment: *This article is dedicated to patient J.S.*

DISCLOSURES

Dr. Ganatra disclosed ownership interest (stock, stock options in a publicly held company) with Abbott Laboratories, AbbVie Pharmaceuticals, Alcon Lab, Anthem, Becton Dickinson, BioMarin, Bristol-Myers Squibb, Dexcom, Eli Lilly, Intuitive Surgical, Johnson & Johnson, Medtronic, Merck & Co, Stryker, and Thermo Fisher Scientific. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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