Pharmacy Friday

Brief pearls related to acute care pharmacology and evidence-based medicine
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- https://sites.google.com/presby.edu/pharmacy-friday

The Treatment of Wernicke's Encephalopathy

Introduction

1. Wernicke's encephalopathy is an acute neuropsychiatric emergency due to thiamine deficiency
2. First characterized by Carl Wernicke in 1881, traditional signs and symptoms of the disorder include altered mental status, ataxia, and ocular signs, including nystagmus and ophthalmoplegia.
3. In the USA it occurs mainly, but not exclusively, in malnourished alcohol dependent patients, or as a consequence of malnutrition from other causes
4. Wernicke's encephalopathy is associated with significant morbidity and mortality, with death reported in up to 17-20% of patients.
5. About 80-85% of patients who survive develop a chronic disorder of severe memory deficits with amnestic states that include learning defects and short term memory loss.
6. Although Wernicke's encephalopathy is difficult to diagnose, thiamine deficiency is common in malnourished patient and repletion has been shown to an effective therapy for patients with Wernicke's encephalopathy and may prevent irreversible neurological damage

Pharmacology	
Thiamine (Vitamin B1)	
Dose	250-500 mg Q8 x3-5 days, then 100 mg daily*
Administration	IVPB over 30 minutes
Formulation	IV/IM/PO
PK/PD	**Distribution:** Highest concentrations found in brain, heart, kidney, liver **Excretion**: Urine mostly as unchanged drug
Adverse Effects	Flushing, diaphoresis, infusion related reactions
Drug Interactions and warnings	No known significant drug interactions
Compatibility	Compatible with NS and D5W
Location in GHS	Drips > 100 mg are compounded in Main Inpatient Pharmacy 200 mg/2 ml vial are located in ED Pyxis
Comments	Protect from light Ethanol may decrease thiamine absorption. Therefore, higher doses may be needed in patients with history of ethanol abuse.

*Dosing is controversial and lack of well-designed RCTs to support dosing strategy

What's the mechanism of action of Thiamine in Wernicke's Encephalopathy?

- Thiamine is an essential cofactor for transketolase, alpha-ketoglutarate dehydrogenase, and pyruvate dehydrogenase in the pathways of carbohydrate metabolism.
- This ultimately leads to the pathologic brain having less ATP due to reduce myelin sheaths, increased lactate, and glutamate accumulation

Do you need to give thiamine prior to glucose to prevent acute psychosis?

- Rationale
  - Thiamine use requirements depend on the metabolic rate and the greatest need for thiamine is during periods of high glucose intake. Therefore giving glucose before thiamine only exacerbates the thiamine deficiency.

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Any Evidence that giving thiamine prior to glucose cause psychosis?

- "Acute Wernicke's Encephalopathy Precipitated by Glucose Loading" by Watson et al.
  - This article describe a case of 4 patients that were given prolonged infusions and large quantities of dextrose range 2-5 days or 2 liter bolus (100g) of D5W before their condition worsened. After the initial exacerbation, each patient returned to his original condition after treated with thiamine. All patients were receiving dextrose infusion for prolonged periods of time period to thiamine..

Where did high dose thiamine (i.e >250-500 mg) dosing come from?

- Prior studies showed that 100-250 mg doses of parenteral thiamine did not prevent death and that Korsakoff's psychosis developed in 56-84% of patients later on follow-up
- One of the current dosing recommendation comes from a 1998 report by Cook et al. which had examined the current literature at the time on WKS, including fourteen studies on thiamine and B-complex vitamin use in Wernicke's encephalopathy.
  - **An intravenous dose of 500 mg three times a day for two consecutive days was recommended which is now recommended by UK Royal College of Physicians Guidelines**

Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Nishimoto, 2017	Case series/ n= 11	IV Thiamine 500 mg q8h 24 x 3-7 days	**73% of patients** (eight out of eleven) had **symptoms of AMS, ataxia, ocular signs, ophthalmoplegia had resolution or improvement after treatment** The median time to initiation of thiamine was 92 h in patients who responded to thiamine vs a median of 90 hr for nonresponders
Ambrose, 2001	RCT/ N=107	IM Thiamine: • 5 vs 20 vs 50 vs 100 vs 200 mg x 2 days	Post-treatment there was a **superior performance** was found in the 200 mg group compared with the other four treatment groups on delayed alternation test.
Baines, 1988	RCT/ n=25	IM thiamine 250 mg Vs PO thiamine 250 mg Vs Placebo	At 24 hr, **only IM treated group was significantly higher than baseline** At 5 days, both groups had almost identical increase in their mean thiamine levels
Thomson, 1983	Case Series	PO thiamine hydrochloride 50 mg Vs PO thiamine propyl disulphide*	Compared to thiamine HCL, thiamine propyl disulphide had ↑ **in blood and CSF levels**, ↓ pyruvate levels, and **improvement in clinical symptoms**

*Fat soluble product with increase bioavailability used to mimic IV formulation

Conclusions

- Patient with chronic alcohol abuse are a group of high risk patients that are at risk for thiamine deficiency (along with other vitamins). These deficiencies are key area in development and treatment in Wernicke 's encephalopathy and korsakoff syndrome, **with intravenous therapies warranted due to minimal absorption for oral route**. There is previous studies that display **that doses <500 mg is inadequate to treat Wernicke's** and Cook et al was one of first to recommend the current IV thiamine 500 mg TID therapy**. If patient are hypoglycemic, glucose should be administered within reasonable close period of time of thiamine.**

References

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