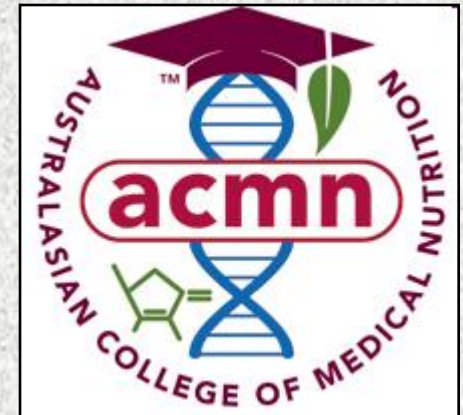


ACMN WORKSHOP

Injectable Nutrients B Vitamins Theory

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Evidence

- The use of high dose B Vits must be based on clinical experience, cases – case series etc. Pharmacokinetic data is based, as usual, on healthy volunteers (outside alcoholism research) and typically is based on low oral doses.

Efficacy

Wernicke's, "Wernicke's at risk",
and related patients.

Efficacy

- The Royal College of Physicians in the UK has published guidelines for using massive doses of vitamins in the treatment of Wernicke's Encephalopathy.

Thomson AD, Cook CC, Touquet R, Henry JA; Royal College of Physicians, London. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and Emergency Department. *Alcohol Alcohol*. 2002 Nov-Dec;37(6):513-21.

Efficacy

- In the 1990s many doctors in the UK had stopped using i.v. therapy for WE, substituting oral thiamine.
- A survey of A&E medicine specialists, psychiatrists and others involved in treating alcoholic patients was conducted to review the current state of knowledge for the treatment of WE.

Efficacy

- WE was more common than previously suspected and many clinicians were confused about the treatment.
- Accordingly, the college developed and published protocols for the appropriate and timely treatment of WE. (Thomson et al.)

Efficacy

- WE is an acute neuropsychiatric condition and on initial presentation it is reversible.
- WE is caused by overwhelming metabolic demands on cells which have depleted intracellular levels of thiamine.

Efficacy

- WE is most commonly seen in alcoholics, and if inadequately treated with thiamine (inadequate = orally or small dose or too late) leads to irreversible changes producing loss of short term memory and impaired ability to acquire new information.

Efficacy

- **WE also commonly occurs in:**
 - Bariatric surgery patients
 - Protein calorie malnutrition (malabsorption or bad diet)
 - Patients with protracted vomiting
 - Bulimia, anorexia
 - Carbohydrate loading with minimal thiamine stores
 - Chronic renal failure
 - Hyperalimentation, AIDS, drug misuse

Efficacy

- In the UK, only 16% of WE patients treated with inappropriately LOW DOSE thiamine (i.e. 50-100mg parenterally) recover fully.
- Death rate with LOW DOSE thiamine is 17-20%.
- 84% with LOW DOSE thiamine develop Korsakoff's Psychosis.

Efficacy

- The **minimum** dose of thiamine required to effectively prevent or treat acute WE in most patients is **>500mg once or twice daily**, given parenterally (IV) for 3-5 days.

Efficacy

- High concentrations are required to achieve significant passive diffusion of thiamine across the BBB. Active transport mechanisms are **insufficient** to treat WE.

Efficacy

- Thiamine replacement must be given immediately. Critical to include magnesium, B6 and B3 B12.
- B Complex and Mg deficiencies and general nutrition depletion are common.

Efficacy

- Supplementation of other water-soluble vitamins, especially nicotinamide and pyridoxine, is advised, since patients at risk for Wernicke's encephalopathy are often deficient in these vitamins. Unless the patient is acutely symptomatic from hypoglycaemia, glucose-containing IV fluids should be avoided before administering thiamine, to avoid precipitating Wernicke's encephalopathy

Efficacy

- Prophylaxis (at risk):
 - B1 250 mg
 - B2 4 mg
 - B6 50 mg
 - B3 160 mg
 - Vit C 500 mgOnce daily by i.v. infusion for 3-5 days

Efficacy

- Established or presumptive diagnosis:
 - B1 500 mg
 - B2 8 mg
 - B6 100 mg
 - B3 320 mg
 - Vit C 1 gby i.v. infusion TDS for 3 days

Efficacy

- With response, back to prophylaxis protocol until clinical improvement ceases.
- Magnesium is a cofactor for thiamine dependent enzymes and is typically depleted in alcoholics and malnourished. *With Mg depletion, thiamine therapy does not work.*

Efficacy

- Suggested adult dose of Magnesium is 35-50 mmol MgSO_4 (~800-1000mg Mg^{++}) in 1L normal saline given over 12-24 hours (RCPL).
- NOT EVER given as a push at these levels

Efficacy

- Note: Larger doses of Vit C (sodium ascorbate) than the RCPL recommended (which is 500 mg TDS) may be appropriate since its essential mechanism is scavenging of free radicals.
- E.g. 15-30g VC daily (acute Wernicke's 30-60g daily – assuming OK renal function)

Efficacy

Historical perspective

Typical clinical applications

Efficacy

- Dr Frederick Klenner (Vitamin C fame) used massive dose of B vitamins in neurological patients, including the treatment of MS. This is compulsory reading!

Klenner FR; Response of peripheral and central nerve pathology to mega-doses of the vitamin B-complex and other metabolites. J. Appl. Nutr. 1973; 25: 16.

Efficacy

- Klenner published several successful cases where megadose B vitamins, along with other high dose nutrients, were used to treat MS and myasthenia gravis.
- The protocol consisted of massive doses of B1 (oral, IV and IM), niacin, B6, B12, Vit C, B2, Vit E, crude liver (injections), AMP, Choline, lecithin, Mg, Ca gluconate, B5 and glycine.

Efficacy

- “The modified “Myers’ cocktail,” which consists of magnesium, calcium, B vitamins, and vitamin C, has been found to be effective against acute asthma attacks, migraines, fatigue (including chronic fatigue syndrome), fibromyalgia, acute muscle spasm, upper respiratory tract infections, chronic sinusitis, seasonal allergic rhinitis, cardiovascular disease, and other disorders.”

Efficacy

- Used commonly in “run down” patients

Efficacy

Table 1. Nutrients in Myers' Cocktail

Magnesium chloride hexahydrate 20% (magnesium)	2-5 mL
Calcium gluconate 10% (calcium)	1-3 mL
Hydroxocobalamin 1,000 mcg/mL (B12)	1 mL
Pyridoxine hydrochloride 100 mg/mL (B6)	1 mL
Dexpanthenol 250 mg/mL (B5)	1 mL
B complex 100 (B complex)	1 mL
Vitamin C 222 mg/mL (C)	4-20 mL

Gaby AR. Intravenous nutrient therapy: the "Myers' cocktail". *Altern Med Rev.* 2002 Oct;7(5):389-403.

Efficacy

- Gaby cites many cases and administration of the Myers' cocktail over an 11 year period of 15,000 injections in 800-1,000 different patients.
- **Folic acid is not added due to precipitation problems.**

Efficacy

- B vitamins are a mandatory part of EDTA Chelation Therapy. Esp B1 increases Pb excretion with EDTA.

Why Injectable?

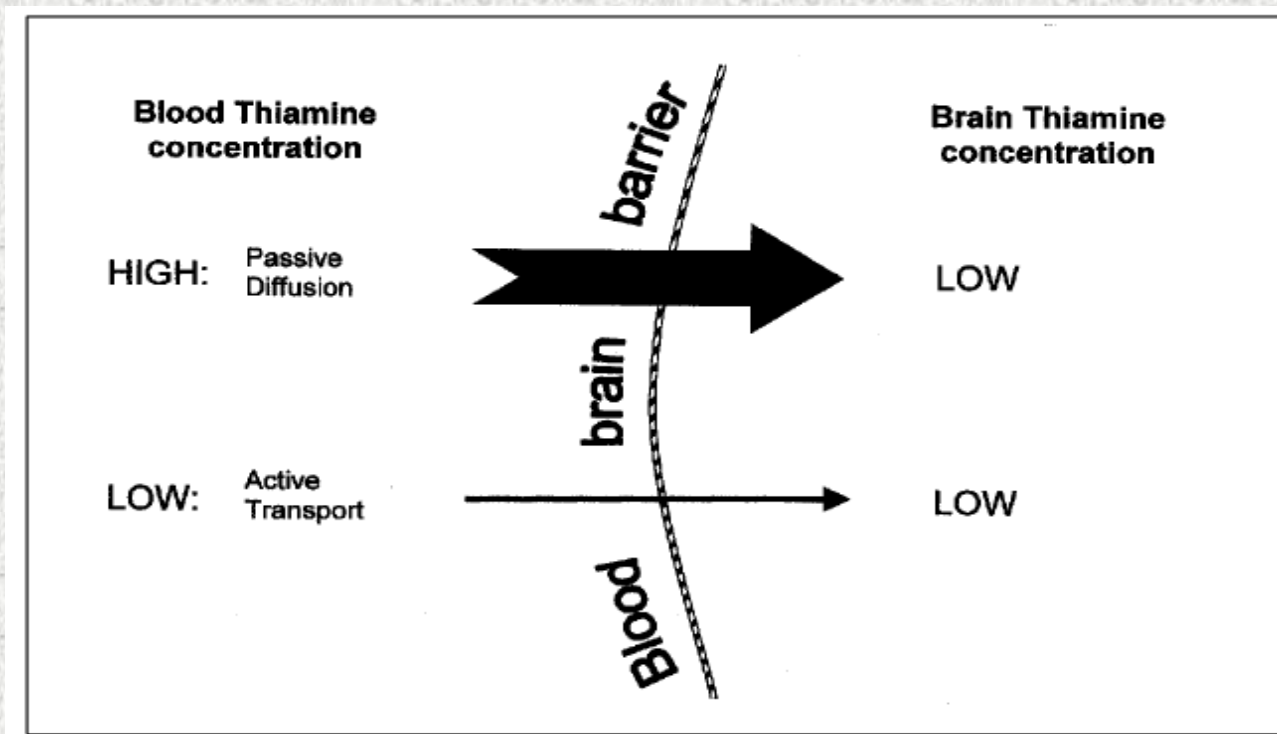
Why Injectable?

- IV administration of nutrients can achieve serum concentrations not obtainable with oral or intramuscular administration
- IV treatment >> marked, transient increase nutrients which provides an opportunity for ailing cells to take up nutrients against a smaller concentration gradient

Why Injectable

- It has already been stated that in severe thiamine depletion, oral B vitamin dosing is insufficient.
- For thiamine in particular, the rate of uptake by active transport (0.3 mcg/hr/g tissue) may be lower than the rate of use in the brain.
- Parenteral thiamine overcomes this via significant passive diffusion.

Why Injectable?



Thompson et al.

Why Injectable?

- Formulation, purity, quality.
- Severe GIT problems, malabsorption
- Dementia, alcoholics, patients with poor compliance for whatever reason.
- An inborn error of metabolism that can be controlled only by maintaining a higher than normal concentration of a particular nutrient
- 100% sure the patient got the dose.
- History of better clinical response.

Safety

Safety

- Significant ADRs to parenteral B vitamins are *extremely rare*. In most cases reactions have been to carriers or additives, such as benzyl alcohol.
- There are however a few true reports of anaphylaxis to several B vitamins, including B1, B6 and B12.

Safety

- “..in 15 years at the Grady memorial hospital in Atlanta (Georgia USA), parenteral thiamine was given > 10,000 times per year in the 1980s and usually by rapid i.v. bolus.”

Safety

- “Similarly in Bellevue hospital, New York, and Denver general hospital, Colorado, > 10,000 i.v. thiamine injections had been given per year over 10 years without any adverse occurrences”

Cook et al.

Safety

- ADRs to other injectable B vitamins are no more commonly reported. These are extremely rare.
- Most ADRs are minor (still rare), pain at injection site, mild pruritus etc.

Safety

- B vitamins are reported to be less likely to produce ADRs if they are injected i.m. or if they are given i.v. as a prolonged infusion. Most problems have occurred with rapid i.v. pushes.
- B vitamins are typically added to chelation bags for slow i.v. infusion – without incident.

Safety

- There is now a long track record of safe use of parenteral B vitamins – many millions of doses.
- Adherence to protocols, use of correct apparatus and aseptic technique all make ADR events very unlikely.

Safety

- N.B. B6 can be toxic if given in large doses continuously ($>1,000\text{mg/day}$ for months). B-Dose Forte contains 100mg Pyridoxine Hydrochloride.
- Injections containing B6 are S4

Protocols

Protocols

- We have already looked at the recommended protocol for i.v. B vitamin administration in WE. The amounts given are chosen because that is what is contained in 2 vials of the parenteral medication available in the UK.
- In Australia, 2 injections (spaced) of B-Dose Forte will provide 500mg thiamine.

Protocols

- Typical RCPL protocol (Australia) for each **500mg** thiamine:

2 vials B-Dose Forte, 1 amp MgSO₄ and 1000 mg Vitamin C can all be mixed in a bag for infusion. The appropriate carrier is NS.

- Typical i.v. infusion is 100mL total volume over 30 mins.

Protocols - Historical

- Klenner used astonishing amounts of B vitamins in thousands of patients (neuropathies):
 - **Thiamin hydrochloride:** 300mg to 500mg (oral), 30 minutes before meals and bed hour, and during the night if awake. The higher amounts in long-standing cases.

Protocols - Historical

- B1 contd. - 400 mg. daily by needle, given intramuscularly. During summer months this can be given every 12 hours to good advantage.
- Two to three times each week, and where office access is convenient, 20 mg. per kg. body weight, or at least 1000 mg. is administered intravenously.

Protocols - Historical

- **Niacin (nicotinic acid):** We recommend 100mg to 3 grams, thirty minutes before meals and at bed hour, and also during the night if awake (all oral) . whichever dose will produce a strong body flush.
- **Pyridoxine (Vitamin B6):** 100mg to 200mg is given before meals and bed hour (oral). At least 100mg daily is given intramuscularly.

Protocols - Historical

- **Cobalamin (Vitamin B12):** 1000mcg. is given three times each week by needle
- **Ascorbic Acid (Vitamin C):** Ten to twenty grams should be taken daily by mouth in divided doses.
- **Riboflavin (Vitamin B2):** 40mg to 80mg given daily by needle IM; 25 mg. before meals and bedtime (oral).

Protocols - Historical

- **Vitamin E**; 800 international units before meals and bedtime must be adhered to in this treatment.
- **Crude liver injections**
- Many more – please see the full paper.

Concerns

Concerns

- All precautions re toxicity should be noted.
- With IV adverse events (rare) are even further minimised by dilution and slower administration.
- Off label use – HIC, Medical Boards etc.
 - Discussed in clinical sessions

Further Reading

- Bowden S, Bardenhagen F, Ambrose M, Whelan G. Alcohol, thiamin deficiency, and neuropsychological disorders. *Alcohol Alcohol Suppl.* 1994;2:267-72.
- Martin PR, Singleton CK, Hiller-Sturmhofel S. The role of thiamine deficiency in alcoholic brain disease. *Alcohol Res Health.* 2003;27(2):134-42. Review.
- Boldorini R, Vago L, Lechi A, Tedeschi F, Trabattoni GR. Wernicke's encephalopathy: occurrence and pathological aspects in a series of 400 AIDS patients. *Acta Biomed Ateneo Parmense.* 1992;63(1-2):43-9.
- Heap LC, Peters TJ, Wessely S. Vitamin B status in patients with chronic fatigue syndrome. *J R Soc Med.* 1999 Apr;92(4):183-5.

Further Reading

- Hoorn RK, Flikweert JP, Westerink D. Vitamin B-1, B-2 and B-6 deficiencies in geriatric patients, measured by coenzyme stimulation of enzyme activities. Clin Chim Acta. 1975 Jun 2;61(2):151-62.
- Langohr HD, Petruch F, Schroth G. Vitamin B 1, B 2 and B 6 deficiency in neurological disorders. J Neurol. 1981;225(2):95-108.