South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Neurological Disorders

EVIDENCE SUMMARY

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QUESTION: The optimum dose of thiamine for prevention and treatment of Wernicke's encephalopathy and chronic alcohol misuse in the acute setting.

Background

In September 2020, a concern was raised by the Western Cape regarding IV administration of thiamine as supplier provides a caution of anaphylaxis in IV use – therefore only recommended for IM use.

The management of suspected alcohol withdrawal/ Wernicke's encephalopathy under 21.2.4 Delirium in the PHC STGs was discussed at an ad hoc NEMLC meeting on 30 September. It was agreed to change the thiamine dose from Thiamine IV/IM 500mg immediately to Thiamine IM 100mg immediately. The decrease in dose was pragmatic, related to poor quality evidence for 500mg, variations in global practice, and thiamine available in 100mg/ml vials and 5ml IM injection unlikely to be tolerable.

At the Adult ERC meeting of 28 October 2020, a query was raised regarding the initial rationale for the 500mg dose with the concern that this was not discussed thoroughly when reducing the dose to 100mg.

High dose IV thiamine is still recommended in the Hospital Adult STGs in Chapter 14 Neurological Disorders: 14.2 DEMENTIA

Wernicke's syndrome: E51.2 + (F02.8*)

- Thiamine, IV, 500 mg 12 hourly for 3 days, followed by 500 mg daily for 3–5 days.
    - Follow with oral thiamine 100 mg 8 hourly.

IV thiamine is also recommended for ethanol poisoning in Chapter 19 (Thiamine, IV, 100 mg in 1 L dextrose 5%) only the dosing of thiamine in prevention and treatment of Wernicke's encephalopathy is considered here.

Introduction

Wernicke's encephalopathy (WE) is an acute neuropsychiatric condition due to overwhelming metabolic demands on cells that have depleted intracellular thiamine (vitamin B_1) resulting in a reversible biochemical brain lesion. It is commonly seen in chronic alcohol misusers, and if treated sub-optimally with thiamine (given by the incorrect route, inadequate dose or too late), leads to irreversible structural changes producing loss of short-term memory and an impaired ability to acquire new information. Failure to treat WE leads to Korsakoff psychosis (KP), a chronic disease characterized by severe memory loss.

In a Royal College of Physicians report,[1] Thomson et al. (2002) note observational evidence suggesting that treatment of WE with low parenteral doses of 50–100 mg of thiamine daily resulted in 16% full recovery, 17–20% died, and 84%

developed KP. Of those with KP, only 21% showed complete recovery; 26% showed no improvement, 28% only slight improvement and 25% showed significant recovery from the amnesic state (can take between 2 months to 10 years). It is therefore essential that thiamine be given as soon as possible in adequate amounts to all patients with suspected or incipient WE. The route of administration must provide sufficient supply of thiamine especially to the dependent enzymes in brain cells. In addition, all hypoglycaemic patients whether or not attributable to chronic alcohol misuse treated with IVI glucose must be given IVI thiamine at the same time to avoid the risk of precipitating WE.

Previous treatment of 500mg IV immediately in the PHC STGs for suspected alcohol withdrawal/ WE and current treatment of WE in Hospital Adult STGs based on empirical clinical practice and uncontrolled trials.[1-3]

Clinical guidelines are vary in recommendations but generally use high doses for treatment (Table 1).[4] NICE recommends thiamine is offered to people at risk of WE 'in doses toward the upper end of the 'British national formulary' (BNF) range' (https://www.nice.org.uk/guidance/qs11/chapter/quality-statement-10-wernickes-encephalopathy)

Summary of the evidence

i) Prevention of WE

Cochrane Systematic Review by Day et al (2013)[5] - one RCT (Ambrose et al., 2001) on prevention of cognitive dysfunction in alcohol withdrawal. 169 patients with alcohol dependence recruited from an inpatient detoxification unit were randomized to receive thiamine doses of 5mg, 50mg, 100mg, or 200mg IM once a day for 2 days. None had signs of WE. 107 patients included in analysis (43 did not complete treatment and data removed for 19 to equate groups for age, sex, and alcohol use). Only 200mg differed significantly from 5mg on cognitive testing post-treatment (mean difference (MD) -17.90, 95% confidence interval (CI) -35.4 to -0.40, P = 0.04).

No further RCTs for prevention or treatment of WE were identified in two recent systematic reviews, one investigating effect of nutritional interventions (McClean et al., 2020)[6] and the other investigating treatment effects on alcohol related cognitive impairment (Caballeria et al, 2020)[7]

ii) Treatment of WE – prevention of Korsakoff's psychosis

The uncontrolled trials noted by Thomson et al. (2002)[1] are not referenced. A citation search of a 2007 Lancet review[8] for trials recommending a minimum dose of 500mg IV three times a day for 3-5 days found reviews but no actual studies or data.

Case-series:

- Nshimoto et al. (2017)[9] – retrospectively reviewed records of 11 patients with suspected or diagnosed WE and who had received high dose thiamine therapy, defined as ≥500mg parenteral thiamine per day. Doses of thiamine varied, including 500mg IV once off, daily, twice a day, and three times a day and duration from 1 to 7 days. Median time to treatment from symptom onset was 92hours. Symptoms resolved in 7 out of 11 patients. No differences observed in those whose symptoms resolved vs those whose symptoms did not in terms of timing of thiamine initiation from symptom onset, patient variables, adverse effects. Conclusion: High-dose thiamine (≥500 mg) appears safe and efficacious for use in patients with suspected WE.
- Soler-González et al. (2014)[10] – describe 10 cases in whom WE had been misdiagnosed and mistreated (time to diagnosis ranged from 2 – 44 days, average 22 days). Three received thiamine at low doses (100mg IM; 300mg oral). All showed at least some degree of improvement with IV thiamine 500 mg/8 h x 3 days, then 500 mg/day x 5 more days with at least 300 mg/day p.o.; some of them suffered severe consequences, mainly Korsakoff's syndrome.

Conclusion

- *Prevention* of WE in alcohol withdrawal/ suspected alcohol withdrawal including hypoglycaemia – 200mg IM/IV should possibly be the minimum dose.

- *Treatment* of WE/ prevention of Korsakoff's – there is no good quality evidence to support 500mg three times a day (recommended in most guidelines – see table 1, below); 500mg once a day IM for 3-5 days, though, may be a pragmatic option.

NEMLC MEETING OF 23 JUNE 2022: NEMLC accepted the proposal to amend the dose of thiamine from "100mg" to "200mg", aligned with available RCT evidence, for the prevention of Wernicke's encephalopathy. NEMLC also deliberated on the route of administration and recommended that for the prevention of Wernicke's encephalopathy, that thiamine should be administered intramuscularly and not by the intravenous route.
NEMLC MEETING OF 8 DECEMBER 2022: • NEMLC accepted the proposal as recommended by the Adult Hospital Level Expert Review Committee (see above)

Table 1. Guideline comparison for prevention and treatment of WE (Latt and Dore, 2014)[4]

Table 2 Some guidelines for thiamine replacement dosage regimen in alcohol-dependent patients with Wernicke encephalopathy/Wernicke Korsakoff syndrome (WE/WKS)

Prophylaxis for patients with suspected WE/WKS or at high risk of WE/WKS	Treatment of patients with a definitive diagnosis of WE/WKS	Reference
(a) 100 mg I/M t.d.s for 3–5 days (b) (UK)250 mg I/M daily for 3–5 days	(a) At least 100 mg I/V for 5 days (b) 500 mg t.d.s for 2 days; if no response, discontinue; if there is response continue with 250 mg I/M or I/V for 5 days	Royal College of Physicians (UK)[3] NB: In the UK , 250 mg thiamine is present in an ampoule of high potency B complex vitamins (Pabrinex)
(a) At least 100 mg I/M for 3–5 days (b) 500 mg I/M daily for 3–5 days (UK) Follow with oral thiamine as an outpatient	(a) At least 100 mg t.d.s I/V for 5 days (b) 500 mg I/V t.d.s. for 2 days; if no response discontinue; if there is response, continue with 250 mg I/m or I/V daily for 5 days, or longer if improvement continues (UK)	*Oxford Specialist Handbooks: Addiction Medicine* (Latt *et al*., 2009).[15]
	200 mg I/M or I/V t.d.s (preferably I/V)	European Federation of Neurological Sciences (EFNS) guidelines (Galvin *et al*., 2010)[5]
(a) For healthy, low-risk patients: >300 mg orally daily (during detoxification) (b) For malnourished/unwell high-risk patients: 250 mg I/M or I/V once daily for 3–5 days, or until no further improvement is seen	>500 mg I/M or I/V for 3–5 days, followed by 250 mg once daily for a further 3–5 days depending on response	British Association for Psychopharmacology (BAP) guidelines (Lingford-Hughes *et al*., 2012)[16]
(a) Low-risk patients: 100 mg orally daily (b) Patients who drink excess alcohol:100–200 mg I/M or I/V daily for 3 days and then 100 mg orally daily	500 mg I/V infusion over 30 min t.d.s for 2–3 days, and then 250 mg I/M or I/V for 3–5 days, or until clinical improvement is seen	Etg Therapeutics Guidelines (http://etg.hcn.com.au/tgc/gig/5209.htn)[17]

Prophylaxis	Treatment of	Reference
	250–500 mg in 100 mL saline over 30 min intravenous infusion t.d.s for 3 days (recommended) or if, less preferred 100 mg I/V once daily 500 mg thiamine I/V infused over 30 min t.d.s. for 2 days and 500 mg I/V or I/M once daily for an additional 5 days in combination with other B vitamins	Wernicke encephalopathy, Best Practice, BMJ Evidence Centre[18] http://bestpractice.bmj.com.acs.hnc.com.au Charness *et al*.[8,9] www.UpToDate.com
(a) For healthy patients with good dietary intake: 100 mg t.d.s orally (b) For chronic drinkers with poor diet: 300 mg I/M or I/V for 3–5 days, followed by 300 mg orally for several weeks	500 mg I/M or I/V for 3–5 days, followed by oral or parenteral thiamine 300 mg for 1–2 weeks	Guidelines for the treatment of alcohol problems Australian Department of Health and Ageing. Commonwealth of Australia (Haber *et al*., 2009)[19]
100 mg IV or I/M on Day 1, and then 100 mg orally daily	100 mg I/V or I/M daily for 3 days and then orally	NSW Drug and Alcohol Withdrawal Clinical Practice Guidelines. Mental health and Drug & Alcohol, NSW Department of Health 2007[20]

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