Wernicke’s Encephalopathy: Role of Thiamine

Wernicke’s encephalopathy, a neuropsychiatric disorder which arises as a result of thiamine deficiency, is a condition frequently associated with alcohol misuse, and has a high morbidity and mortality. In 80% of cases, the diagnosis is not made clinically prior to autopsy and inadequate treatment can leave the patient with permanent brain damage: the Korsakoff syndrome. Recommendations are provided for the prophylactic treatment of Wernicke’s encephalopathy as well as the treatment of the suspected or diagnosed case.

INTRODUCTION

Wernicke’s encephalopathy (WE) is an acute neuropsychiatric disorder which arises as the result of an inadequate supply of thiamine to the brain. It can occur in the context of inadequate dietary intake, and is also seen in a number of medical conditions associated with excessive loss of thiamine from the body, or impaired absorption of thiamine from the intestinal tract (1) (Table 1).

In the developed world, WE is most commonly associated with alcohol misuse. Early and adequate treatment with thiamine, by the appropriate route, can reverse the induced biochemical changes in the brain and prevent the development of structural lesions; failure to treat results in permanent brain damage called the Korsakoff Syndrome (KS) (1). WE that is not associated with alcohol misuse can usually be treated with smaller oral doses of thiamine. These patients rarely develop KS, indicating that the combined effect of thiamine deficiency and alcohol misuse produces a synergistic effect which is much more detrimental than either alone (2,3).
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HOW COMMON IS WERNICKE’S ENCEPHALOPATHY?

WE is not diagnosed prior to autopsy in 80% of cases. Clinicians fail to diagnose the syndrome, perhaps in the belief that it occurs less commonly than it does (1,4). Autopsy studies have shown that Wernicke lesions were present in 1.4% of general medical patients, increasing to 12.5% in known “alcoholics” and to 35% in “alcoholics” with cerebellar damage (1,5). The reduction in the number of autopsies being carried out worldwide has denied us this gold standard by which to judge the incidence of WE, but it is unlikely to have declined (2).

THE DEVELOPMENT OF WERNICKE’S ENCEPHALOPATHY

The thiamine requirement for healthy individuals is related to their carbohydrate intake and is between 1–2 mg per day: this requirement increases with alcohol (continued on page 24)
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misuse. The body can only store between 30–50 mg of thiamine, thus body stores of individuals on a thiamine deficient diet are likely to be depleted in four-to-six weeks. Further thiamine deprivation causes a significant decrease in the activity of many enzymes which play a key role in metabolism (9).

However, diets are rarely totally devoid of thiamine and the time it takes for significant thiamine depletion to develop will vary. During the initial phases of deprivation, the thiamine deficit can be corrected by oral supplementation. Individuals with alcohol misuse problems are, however, at particular risk of developing thiamine deficiency. As their drinking progresses, so alcohol, often high in carbohydrate and with low or absent amounts of thiamine, is substituted for food. With the onset of alcohol-related liver damage the ability to store thiamine in the liver is progressively reduced. An already compromised nutritional state may be further exacerbated by diarrhea, steatorrhea and vomiting (10) (Figure 1).

As these changes continue, oral thiamine becomes less effective as a therapeutic agent. Finally, oral thiamine taken as medication or as food, is inadequate, as both continuing heavy alcohol use and malnutrition interfere with absorption of thiamine from the GI tract (10,11).

In order for dietary thiamine to become active in brain cells, it must undergo at least four transport steps. It is first taken up by the brush border of the intestine and then exported by the enterocyte into the blood. In man this requires an active, saturable, stereospecific and sodium-dependent transport mechanism. This mechanism limits thiamine absorption in health to no more than 4.5 mg–5.6 mg per oral dose greater than 15 mg. Absorption can decrease to less than 1.5 mg per oral dose in the abstinent, but malnourished alcoholic,
or less if he is also intoxicated (1). Thiamine must then cross the blood-brain barrier to reach the neurons and finally it must be transported into the mitochondria and nuclei of the neurons. See Guerrini, et al for further discussion about thiamine transporters (12).

**MAKING THE DIAGNOSIS**

Studies have reported that circulating levels of thiamine are reduced in 30%–80% of alcohol misusers. Deficiencies in folate, pyridoxine and riboflavin are also reported in alcohol misusers (1). Nicotinic acid deficiency occurs much less frequently, but has been reported to be associated with brain damage (13).

Recently, an improved analytical procedure for the determination of thiamine and its esters in erythrocytes was used to analyze a group of alcoholic patients in the United States (14,15). The data, obtained by direct measurement of thiamine (T), thiamine monophosphate (TMP), and thiamine diphosphate (TDP) content in human erythrocytes, confirmed that T and TDP levels in alcoholics were significantly lower than in controls, thereby documenting a marked reduction in the thiamine stores in chronic alcoholics. However, WE cannot be diagnosed by measuring the circulating thiamine level since there is not one critical circulating level below which every individual will develop the Wernicke lesion. This indicates that other factors may also play a part (e.g. thiamine utilization) and the thiamine level only confirms that the patient is seriously at risk. It usually takes several days to obtain the results of a thiamine level, whatever test is used, and it is important not to delay treatment since WE is an emergency. The physician must rely upon clinical information to recognize patients at risk of developing WE or to make a presumptive or definitive diagnosis of WE (2).

**CLINICAL SIGNS AND SYMPTOMS OF THIAMINE DEFICIENCY**

In 1881 Wernicke drew attention to what has come to be called the “classic triad” of signs and symptoms of WE: oculomotor abnormalities, cerebellar dysfunction and confusion (2,16) (see Figure 2).

However, Clive Harper and his group demonstrated that only 16.5% of patients presented with all three signs and many presented with confusion alone (17). Caine, et al developed “operational criteria” to differentiate between WE alone or in combination with KS or hepatic encephalopathy (HE) (18). They proposed using two of the following signs:

- Dietary deficiencies
- Oculomotor abnormalities
- Cerebellar dysfunction
- Either altered mental state or mild memory impairment.

Using these criteria, ante-mortem identification of WE can be achieved with a high degree of specificity, although this is reduced in the presence of hepatic encephalopathy. Neuro-imaging can be helpful since in most chronic cases, the MRI scan will show evidence of mammillary body atrophy and enlargement of the third ventricle (19).

Important as these criteria are in the diagnosis of WE, it is essential to identify patients at risk of devel-
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There may be serious problems with patient compliance. Baker, et al have confirmed that both thiamine and vitamin B₆ in food are poorly available to the alcoholic patient with liver disease (20). It is therefore not surprising that cases of WE have been described in alcoholics taking high dose B vitamin supplementation orally (21). Of particular concern are alcohol dependent patients undergoing medically assisted withdrawal from alcohol, who should also be given prophylactic thiamine since there is an increased requirement for thiamine at this time (4). Malnourished, malnourished patients treated with a high protein, vitamin supplemented diet, have been shown to absorb thiamine normally after six-to-eight weeks (10).

It is recommended that patients at risk should receive 250 mg of thiamine IM daily for a minimum of three-to-five days (22). This dose of thiamine has not been determined by randomized double-blind controlled studies but from empirical clinical practice and has been recommended by the Royal College of Physicians, London (4). Please see references (1) and (23) for further discussion.

Anaphylactoid reactions may occur very occasionally following administration of parenteral thiamine. A history of asthma, atopy and other allergies should be obtained, a record card given to the patient and a central record kept of the administration. Adverse reactions are less common with the IM preparation and are more likely to occur after multiple administrations or when given IV as a bolus. Resuscitation facilities should be available on site (22).

TREATMENT OF PATIENTS IN WHOM A PRESumptive OR ACTUAL DIAGNOSIS OF WE HAS BEEN MADE

A presumptive diagnosis of WE should be made when there is a history of alcohol misuse associated with the symptoms shown in Figure 3.

These patients, together with those in whom a definite diagnosis of WE has been made, should be given 500mg of thiamine hydrochloride IV three times a day for two-to three days, diluted in 50–100 mL of normal saline, and infused slowly over 30 minutes to reduce the chance of an anaphylactic reaction (Table 3).

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Treatment should then follow as indicated in Figure 3. The dose required to treat patients with WE is not based on evidence from randomized controlled clinical trials. With our present but limited knowledge, it would be unethical for such trials to be carried out. The treatment has been determined from the following evidence:

- Cases of WE have been described in patients taking high doses of oral thiamine (1).
- Doses of parenteral thiamine between 100 mg–250 mg do not always prevent death and between 56%–84% of patients with WE are found to develop KS if followed up long-term (2,8,24). This poor outcome is not necessarily due to irreversible brain damage having been present at the time of presentation. Other studies show that these doses are sub-optimal and may not restore vitamin status, or improve clinical signs or prevent death (1).
- There are case reports of patients requiring up to 1 gm of thiamine in the first hours to achieve a clinical response (1,25,26).
- The doses of thiamine in Figure 3/Table 3 are recommended by the British National Formulary and the Royal College of Physicians, (London) (6,23,27) and have been licensed for use in the UK by the Medicines and Healthcare Products Regulatory Agency (MHRA) since 1994. They are also in accordance with the evidence-based guidelines published by the British Association for Psychopharmacology (28). A recent publication by Charness from Harvard Medical School (US) (2009) suggested that these recommendations should be considered for adoption in the US (29). Two recent reviews have emphasized the need to determine the optimum dose of parenteral thiamine for the prophylaxis and treatment of Wernicke’s encephalopathy (6,30).
Doctors choosing to use lower doses of thiamine run the risk of under-treating some patients, although this may not be apparent unless the patient is followed up for an adequate period of time and their neuropsychological status tested appropriately.

As the intravenous administration of glucose can precipitate WE in thiamine-deficient individuals, intravenous thiamine should always be administered before or at the same time as intravenous glucose. This is essential for patients who have been drinking alcohol and present with hypoglycemia (29).

Adverse reactions to parenteral thiamine occasionally occur and it is important that clinicians are prepared to deal with them. However, many hospitals have given parenteral thiamine for many years without any serious reactions. In Wrenn and Slovis’ series, 989 consecutive patients were treated with 1,070 doses of thiamine, resulting in only one major reaction of general pruritus (31). In 1992 the same authors reported that more than 300,000 patients had been treated with parenteral thiamine without any significant allergic reactions (32).

CORRECTING OTHER NUTRITIONAL DEFICIENCIES

It is important to remember that all patients with a presumptive or definite diagnosis of WE may have multiple nutritional deficiencies that will need to be corrected, in order to replenish vitamin stores and optimize metabolic balance. For example, adults will often require magnesium 10–30 mEq/day, potassium 60–180 mEq/day and phosphate 10–40 mmol/day (4,33). Magnesium is an important co-factor in many thiamine dependent enzymes involved in carbohydrate metabolism, and patients may fail to respond to parenteral thiamine in the presence of hypomagnesemia (4). The systemic effects of excessive alcohol increase the susceptibility to, or directly cause important disorders in the critically ill. The reader is directed to the Lancet review article by Moss and Birnham (34).

REFERENCES

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