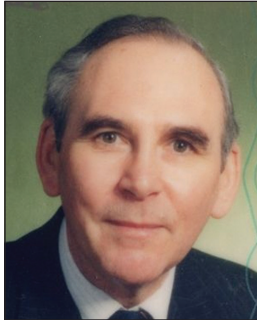


Carol Rees Parrish, R.D., M.S., Series Editor

Wernicke's Encephalopathy: Role of Thiamine



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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

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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).

Table 1
Some clinical conditions which may co-exist with alcohol use disorders, causing patients to be at additional risk of developing Wernicke's Encephalopathy

- Protein-calorie malnutrition from malabsorption
- Anorexia nervosa
- Intravenous infusions including total parenteral nutrition without adequate thiamine
- Refeeding syndrome
- Patients with protracted vomiting including pregnancy, toxemia
- Teenage pregnancy with poor nutrition/drug misuse while mother still growing
- Carbohydrate loading IV/oral when thiamine stores are minimal
- Diabetic ketoacidosis
- Chronic renal failure, dialysis
- AIDS, drug misuse
- Patients on diuretics for ascites
- Partial gastrectomy, gastrectomy or gastric stapling, gastric bypass, gastric or esophageal carcinoma, widespread carcinomas
- Severe obesity, ulcerative colitis, pernicious anemia
- Prisoners admitted to police cells, prison; individuals who are homeless or living in hostels
- Patients with Alzheimer's disease or neglect in old age, especially if living alone
- Chronic schizophrenia
- Widespread tuberculosis
- Thyrotoxicosis (very high thyroid hormone levels)
- Increased requirements caused by fever, pregnancy and adolescent growth
- Thiaminases are enzymes that break down thiamine in food (found in raw freshwater fish, raw shellfish, etc.—e.g. Japan)
- Genetic abnormality of transketolase enzyme

In this paper we concentrate on the management of patients with alcohol misuse who present with WE. We discuss clinical presentation, appropriate treatment and how to prevent the development of permanent brain damage from KS.

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).

FAILURE TO TREAT WERNICKE'S ENCEPHALOPATHY

Wernicke's encephalopathy is a medical emergency. Untreated, it leads to death in up to 20% of cases (5), or, in 85% of the survivors, to the chronic form of the condition, the Korsakoff syndrome. Some 25% of the Korsakoff group will require long-term institutionalization (6,7).

The characteristic neuropathology of WE involves neuronal loss, micro-hemorrhages, and gliosis in the paraventricular peri-aqueductal grey matter and in the mammillary bodies (8). The amnesia of KS is probably due to the interruption of diencephalic-hippocampal circuits involving the thalamic nuclei and the mammillary bodies (9).

Clinically, "KS" is characterized by a memory disorder, occurring in clear consciousness, such that the patients appear to be entirely in possession of their faculties. However, they show a severe impairment of current and recent memory, repeatedly asking the same questions over and over again, and failing to recognize people they had met since the onset of the illness. The illness seems to affect mainly the consolidation of recent memory traces more than remote memories, but the impairment may involve memories from up to 30 years before. Sometimes, affected individuals fill the memory gaps creating "false memories" (confabulations); these false recollections often represent real memories jumbled up and recalled out of temporal sequence.

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

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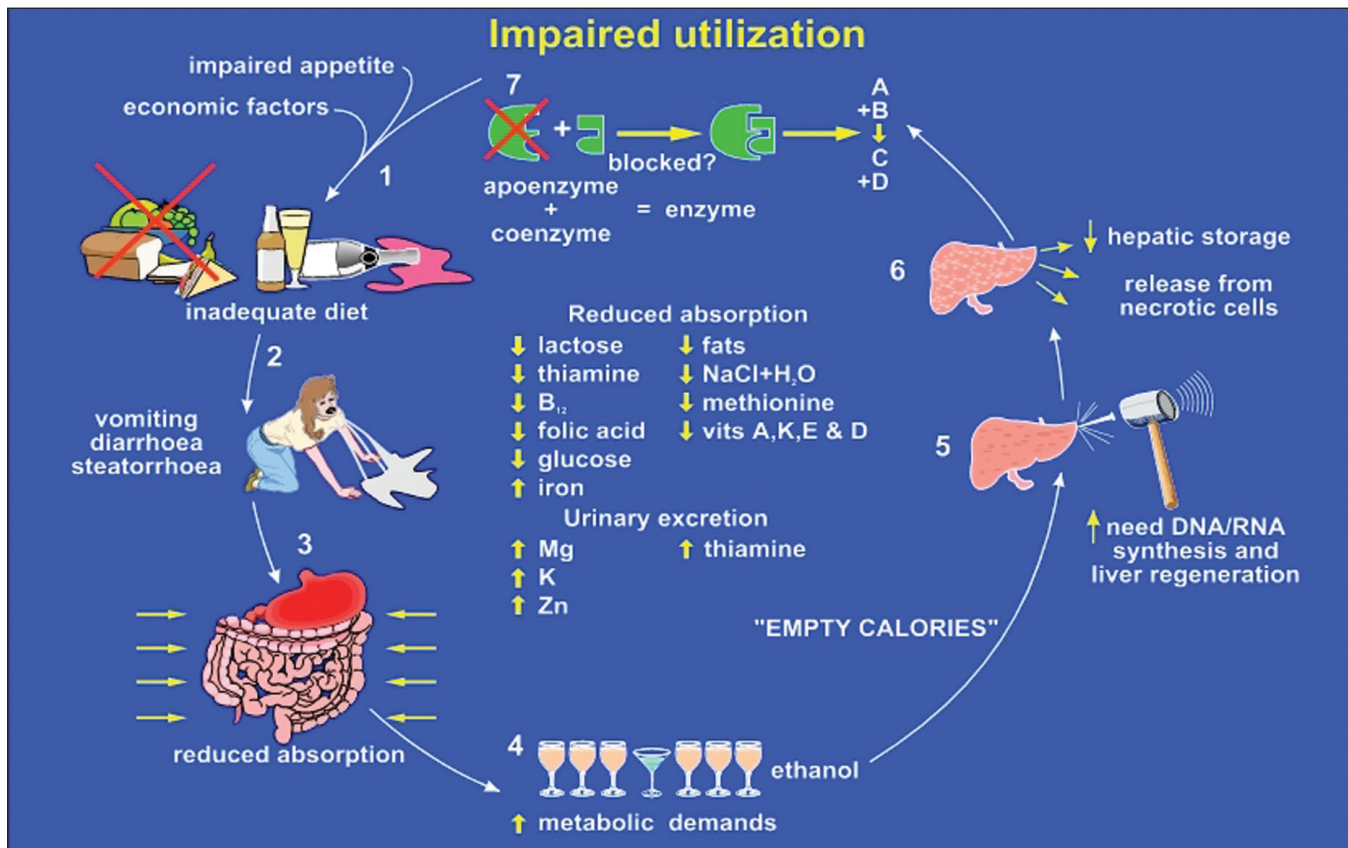


Figure 1. Mechanisms of nutritional deficiency in alcohol misuse. Reproduced from Thomson (2000) reference (10) by kind permission of Oxford University Press.

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,



Figure 2. Patient with (a) Ophthalmoplegia due to Wernicke's encephalopathy (left); (b) six hours after IV thiamine hydrochloride (right).

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-

Table 2
Clinical evaluation of patients at risk of thiamine deficiency*

Clinical history

- Weight loss in past year
- Reduced Body Mass Index
- General clinical impression of patient's nutritional status
- High dietary carbohydrate intake
- Recurrent episodes of vomiting in past month
- Co-occurrence of other nutritionally related conditions (polyneuropathy, amblyopia, pellagra, anemia)

Early signs-symptoms of thiamine deficiency

- Loss of appetite
- Nausea/vomiting
- Fatigue, weakness, apathy
- Giddiness, diplopia
- Insomnia, anxiety, difficulty in concentration
- Memory loss

Later signs-symptoms

- Classic triad: oculomotor abnormalities, cerebellar dysfunction (ataxia) and confusion
- Quiet global confusion with disorientation in time/place
- Confabulation/hallucinations
- Onset of coma

*Patients may present with different combinations of symptoms and signs

oping WE as early as possible and not to take the chance of allowing serious tissue damage to occur in the brain. With this in mind, we have recently reviewed 15 studies carried out over the past 125 years in which both the observed signs/symptoms were recorded during the patient's illness and the diagnosis of WE confirmed subsequently at autopsy (2). The early signs and symptoms associated with thiamine deficiency occur whether the patients are also alcohol misusers or have thiamine deficiency alone, and are listed in Table 2, together with predisposing factors to deficiency. This list should help clinicians to decide whether patients are at risk of becoming thiamine deficient.

TREATING PATIENTS AT RISK

Oral thiamine hydrochloride cannot be relied upon to treat patients at risk of WE and even if this were tried,

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). Malabsorbing, 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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Wernicke's Encephalopathy

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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).

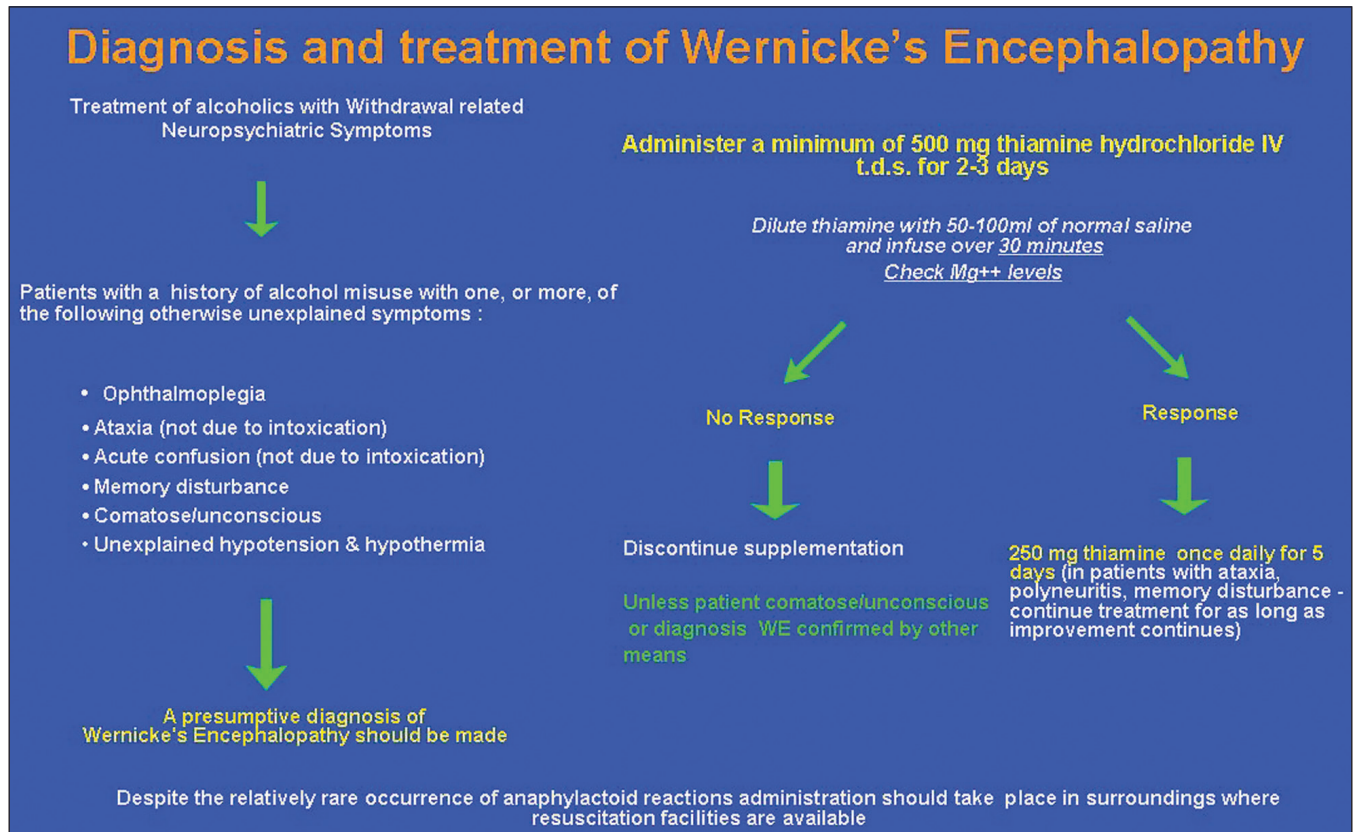


Figure 3. The Diagnosis and Treatment of Wernicke's Encephalopathy

Table 3
The Immediate Treatment of Wernicke's Encephalopathy

- Thiamine 500 mg IV t.i.d. for 2-to-3 days and 250 mg daily for the next 3-to-5 days given over 30 min. diluted in 50–100 mL of normal saline
- Thiamine 100 mg p.o. t.i.d. for the rest of the hospital stay and during outpatient treatment. Absorption will be <4.5 mg daily (10)
- Multivitamins IV
- Replace magnesium: average deficit 2 mEq/kg
 - Replace as outlined by Flink, 1969 (33): check renal impairment.
- Replace fluid and electrolyte losses: monitor electrolytes, blood pressure and renal function

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).

SUMMARY AND CONCLUSIONS

Wernicke's encephalopathy is a common condition caused by thiamine deficiency. It is frequently undiagnosed prior to autopsy and is associated with high morbidity and mortality. Oral thiamine is poorly absorbed and ineffective in chronic alcohol misusers both for prophylaxis and treatment of Wernicke's encephalopathy. It is important not only to correct the thiamine and magnesium deficiencies, but also to correct all other nutritional deficiencies in order to give the patient the best opportunity to recover normal brain function. Further work is essential to determine the optimum dose of thiamine required to prevent permanent brain damage (KS). In view of the diagnostic difficulties, clinicians should have a low threshold for making a "presumptive" diagnosis of Wernicke's encephalopathy. It is better to give too much thiamine too soon than to give too little too late (35). ■

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