Alcohol & Alcoholism Vol. 41, No. 2, pp. 159–167, 2006 doi:10.1093/alcalc/agh250
Advance Access publication 29 December 2005

THE TREATMENT OF PATIENTS AT RISK OF DEVELOPING WERNICKE'S ENCEPHALOPATHY IN THE COMMUNITY

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(*Received* 21 *December* 2004; *first review notified* 16 *February* 2005; *in revised form* 1 *November* 2005; *accepted* 2 *November* 2005; *advance access publication* 29 *December* 2005)

Abstract — Aim: To review the process of identifying alcohol-dependent patients at risk of developing Wernicke's encephalopathy (WE) in the community, and prophylactic treatment options. **Methods:** Non-systematic literature review of the diagnosis of thiamine deficiency and of its treatment in the community. The role of supplementation of beer and bread with thiamine was evaluated. **Results:** The diagnosis of thiamine deficiency is not always made, and treatment apparently may sometimes be inadequate. **Conclusions:** Alcohol-dependent patients in the community who are at risk of developing WE should be given thiamine 250 mg, intramuscularly, daily for 3–5 days as part of a community detoxification programme. Further work is essential to determine the optimum dose of thiamine required to prevent permanent brain damage (Korsakoff's Psychosis). Neurotoxicity, due to the metabolism of excessive alcohol in patients with chronic and severe alcohol dependence, must be considered as an important factor in determining the long-term outcome of treatment.

INTRODUCTION

There is considerable evidence that Wernicke's encephalopathy (WE) is under-diagnosed and inadequately treated in the community. It became apparent in the mid-1990s that many doctors in the UK had stopped using intravenous (IV) thiamine therapy and had substituted oral thiamine even in some patients believed to have WE (Cook *et al*., 1998; Hope *et al*., 1999; D. Taylor and J. Marshall; personal communication). We have recently been contacted by a number of doctors from different countries seeking guidance on the best treatment for WE, especially in the community. All expressed anxiety at the intermittent interruption in the supply of thiamine in its various forms and at the limited pharmacological doses available in their countries. Recently these concerns have prompted a letter in *Alcohol and Alcoholism* (Agabio, 2005).

This paper examines the evidence for inadequate treatment of WE in the community and presents guidelines to help identify such patients at risk of developing WE to monitor their ongoing nutritional state and to provide safe prophylactic treatment where indicated.

ARE PATIENTS AT RISK OF WERNICKE'S ENCEPHALOPATHY BEING IDENTIFIED OR ADEQUATELY TREATED IN THE COMMUNITY?

We do not know how often patients with alcohol problems in the community unnecessarily suffer brain damage. Even in hospitals 80% of patients with WE are not identified prior to death, and the diagnosis is only then established if a specific search is made for the lesions at post-mortem (PM) (Torvik *et al*., 1982; Reuler *et al*., 1985; Victor *et al* 1989). Careful PM studies of 26 691 patients in general hospitals from different countries demonstrated the WE lesion in 1.4% of patients examined: in those misusing alcohol this figure increased to between 12.5 and 35% (Torvik *et al*., 1982; Harper *et al*., 1995; Cook *et al*. 1998).

Very few PM studies looking for WE lesions in individuals dying in the community have been carried out, although circumstantial evidence is strong that many will be at risk (Table 1). Harper *et al*. (1989) carried out a prospective neuropathological study of the prevalence of WE in 285 autopsies from a defined area of Sydney. The reported prevalence of 2.1% was similar to that found in larger hospital studies in Australia (2.8%) but higher than for most other cities: New York (1.8%), Oslo (0.8%) (Harper *et al*., 1995). These rates are still unacceptably high and are likely to increase, given current drinking practices.

In 1996, the first national census of alcohol treatment agencies in the UK estimated that 10 000 individuals were seen for treatment or advice on the census day with two-thirds of the clients being seen by the voluntary (non-statutory) sector (Luce *et al*., 1998). Some voluntary agencies use the services of part-time general practitioners (GPs) but most do not have any medical input. Hospital doctors frequently fail to diagnose thiamine deficiency (Lancet, Editorial, 1998). Signs and symptoms are not a reliable guide to diagnosis (Torvik *et al*., 1982; Reuler *et al*., 1985; Harper, 1986; Blansjaar and van Dijk, 1992) and Korsakoff's psychosis (KP) may be difficult for non-specialists to differentiate from other causes of dementia. Many cases of KP remain undiagnosed especially in impoverished areas of large cities, within nursing homes, boarding houses, or among other itinerant individuals (Price *et al*., 1987). Often residents of 'wet houses', most of whom have a degree of brain damage, are allowed to continue drinking. How can we be confident that patients at risk of WE in the community are receiving the treatment that they need?

FAILURE TO PROVIDE ADEQUATE TREATMENT

Not only is it difficult to identify the patient at risk of developing WE, but there is also evidence that specialists may not

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Table 1. Prevalence of serious alcohol misuse in UK

- 150 000 hospital admissions per year (Strategy Unit, 2003)
- 15–22 000 deaths per year (Strategy Unit, 2003)
- 78 000 admissions to NHS hospitals for mental or behavioural disorders associated with alcohol misuse (Strategy Unit, 2003)
- 23 000 admitted with acute intoxication (Strategy Unit, 2003)
- 30 000 hospital episodes for alcohol-dependence syndrome
- 1/3 of all A & E attendances (Strategy Unit, 2003; Royal College of Physicians, 2001)
- 20% general hospital admissions have alcohol-related problems (Strategy Unit, 2003; Royal College of Physicians, 2001)
- Peak age for alcohol-related deaths men and women 1991 was: 70 years and is in 2000: 55–70 years (Strategy Unit, 2003)

always provide the appropriate treatment even when a diagnosis is made. A survey of psychiatrists and accident and emergency specialists in the UK showed no consensus as to which vitamins might be beneficial, nor the best method of administering them. (Hope *et al*., 1999). These findings confirmed the results of a survey conducted in 1994 on the methods of thiamine replacement for alcohol dependence in 273 hospitals in England and Wales (Table 2). The findings showed a shift towards the use of oral supplements and decreased use of parenteral vitamins for all indications, including suspected and confirmed cases of WE. (D. Taylor and J. Marshall; personal communication). Simple guidelines based on an understanding of the natural history of the condition would allow patients at risk to be identified and adequately treated.

Table 2. Number of hospitals using oral and parenteral thiamine before withdrawal of Parentrovite and after the introduction of Pabrinex

	Before withdrawal of Parentrovite		After introduction of Pabrinex	
	Oral *n* (%)	Parenteral *n* (%)	Oral *n* (%)	Parenteral *n* (%)
Admitted for observation	54 (58)	39 (42)	109 (93)	8 (7)
Suspected severe vitamin deficiency	22 (18)	99 (82)	99 (69)	45 (31)
Suspected WE	5 (5)	90 (95)	27 (23)	90 (77)
Confirmed WE	3 (3)	90 (97)	27 (23)	90 (77)

Includes information from all questionnaires. From Taylor and Marshall, personal communication.

IDENTIFICATION OF PATIENTS AT RISK

If facilities were available to monitor circulating thiamine levels on a regular basis, alcohol-dependent individuals thought to be at risk of developing WE could be treated with oral thiamine and further tests carried out to see if they had responded to the therapy, assuming that they were compliant. Recently, Maschke *et al*., (2005) found that 30% of a sample of chronic alcoholic subjects had signs of cerebellar ataxia and that 27–42% of the brains showed vermal atrophy as measured by MRI brain scan. Vitamin B1 levels correlated with cerebellar size and the results supported the view that thiamine deficiency rather than the direct neurotoxic effects of alcohol was the main cause of cerebellar degeneration. This underlines the need for early and effective treatment with thiamine in alcohol-dependent individuals. In general, however, the greater the degree of malnutrition and the more severe the alcohol misuse/dependence the more likely the patient is to develop WE (Table 1).

The evidence for thiamine prophylaxis during alcohol withdrawal has previously been set out (Thomson and Marshall, 2005). The majority of alcohol-dependent individuals can safely undergo medically assisted withdrawal in the community (Edwards *et al*., 2003). A risk assessment should be carried out to decide whether outpatient or community withdrawal is appropriate. The severity of the alcohol-dependence syndrome and a number of other factors may point towards inpatient treatment. These factors will now be discussed.

The presence of the following factors should preclude treatment for alcohol withdrawal in the community:

(i) delirium tremens or a history of delirium tremens;
(ii) a definitive diagnosis of WE or a presumptive diagnosis of WE. This diagnosis should be made when there is a history of alcohol misuse with one or more of the following otherwise unexplained symptoms:
  - Ophthalmoplegia;
  - Ataxia (not due to intoxication);
  - Acute confusion (not due to intoxication);
  - Memory disturbance;
  - Comatose/unconscious;
  - Unexplained hypotension and hypothermia;
(iii) Severe alcohol dependence; (ICD 10 Diagnosis; WHO, 1992); a score of >30 on the Severity of Alcohol Dependence Questionnaire; (SADQ, Stockwell *et al*., 1983);
(iv) Severe concurrent physical or mental illness (including cognitive impairment); see Table 1;
(v) A history of seizures;
(vi) Repeated unsuccessful attempts at medically assisted withdrawal/detoxification; this is based on clinical experience rather than hard research evidence.

However, there will be patients in the community who remain at risk of WE. These include:

(i) Patients undergoing a community-based alcohol-withdrawal/detoxification programme, because they refused inpatient admission;
(ii) Patients undergoing a community-based alcohol withdrawal/detoxification programme for whom inpatient treatment would have been indicated if it had been available;
(iii) Patients undergoing a community-based alcohol withdrawal/detoxification programme who develop any unexplained neuropsychiatric symptoms should be treated as inpatients;
(iv) Patients undergoing an alcohol withdrawal/detoxification programme who develop hypotension and hypothermia;
(v) Patients undergoing a medically assisted alcohol withdrawal/detoxification programme who refuse parenteral thiamine.

There will also be a number of alcohol-dependent individuals who develop WE that goes unrecognized, who could be protected with adequate prophylaxis. Such individuals include detainees admitted to police cells, prison, individuals living intermittently in hostels, drug addicts, etc.

WHAT ARE THE THERAPEUTIC OPTIONS?

The Royal College of Physicians (2001) report entitled 'Alcohol — can the NHS afford it?' recommended the following thiamine regimen:

> 'To prevent neuropsychiatric complications of vitamin B deficiency in patients undergoing alcohol withdrawal in the community, high dose oral thiamine, (200 mg/day) together with vitamin B strong tablets (30 mg/day) is the treatment of choice'. (Royal College of Physicians, 2001; p34)

This may not be adequate since the evidence indicates that, in healthy individuals, a maximum of only ~4.5 mg of thiamine will be absorbed from any oral dose >30 mg. If the thiamine is given in divided doses, then there is the problem of compliance (Price *et al*., 1987). In a group of malnourished alcohol-dependent individuals, the total absorption of thiamine was reduced to approximately one-third of the control value. The treatment of patients with WE using 50 mg of oral thiamine hydrochloride was totally ineffective, failing to increase the circulating level of thiamine and the cerebrospinal fluid (CSF) concentration, and producing no improvement in the ophthalmoplegia or the confusion, (Thomson *et al*., 1971; Thomson, 2000). This raises the question as to whether oral therapy is appropriate in malnourished patients, especially if they continue to drink alcohol! It must be remembered that some of the oral dose will be excreted before it is stored or utilized and that depleted tissues throughout the body will be competing for the available thiamine. Furthermore, alcohol may be present in the early stages of withdrawal and may interfere with absorption of thiamine. With the increased (metabolic) activity during delirium tremens, the muscles, kidneys, liver, etc. will begin to burn up more glucose, thereby using some of the limited available circulating thiamine. Rapid transport of thiamine into the brain by diffusion will depend on a high plasma-to-brain ratio, which is probably not obtained by oral doses. It has been suggested that the daily requirement for thiamine to maintain 'neural integrity' is ~0.5 mg daily (Brody, 1999; Eitenmiller and Laden, 1999; Stacey and Sullivan, 2003). Supporting the facts previously stated, the consensus is that generally 'two-thirds of orally ingested thiamine is not absorbed or processed into its usable form by heavy alcohol misusers' (Price and Kerr, 1988; Victor *et al*., 1989; Harper *et al*., 1998; Todd *et al*., 1999). As part of an attempt at primary prevention, Price carried out a cross-national comparison of the frequency with which drinkers who were interviewed in detoxification and rehabilitation units in Queensland, Australia and Merseyside, UK were taking supplementary vitamins while continuing to drink. This study was carried out in 1983. Of the 90 UK subjects, only 3 were taking vitamins regularly, 22 were taking them intermittently, and 65 never took them. Following widespread publicity given by the media in Australia between 1979 and 1980 to fortify beer with thiamine and to explain the reasons why this was necessary, 46% of Queensland problem drinkers were taking supplementary thiamine in 1983, but this had fallen to 28% by 1986 (Price, 1985; Price *et al*., 1987).

It would, therefore, seem that oral therapy cannot be relied upon for the treatment of at-risk groups of patients e.g. significant weight loss, poor diet, signs of malnutrition, long history of alcohol misuse, etc. It has also been found that some patients with WE require at least 1 g of thiamine IV within the first 24 h (Cook *et al*., 1998). This may be owing to damage to the apoenzymes, because of problems with the blood-brain barrier (Schroth *et al*., 1991) or genetic abnormalities, possibly due to genetically different enzymes or different metabolic pathways with increased requirements (Heap *et al*., 2002). The critical blood concentrations of thiamine for treating WE have not been determined.

CAN THIAMINE PROPYL DISULFIDE HELP?

Thiamine propyl disulfide is a lipid form of thiamine, which is absorbed from the intestine by diffusion, provides blood levels similar to IV thiamine administration, and delivers high levels to the brain (Thomson *et al*., 1971). An oral preparation called Thiasure is a multivitamin/multimineral dietary supplement that contains 50 mg of thiamine propyl disulfide, together with other important nutrients such as folic acid, vitamin B12, B6, and magnesium. It is made by Recovery Pharmaceuticals in the USA. Thiamine propyl disulfide has been widely used in Japan since the 1950s and a similar product is available in Germany (Milgamma mono 150 is a benfotiamine from Worwag Pharma).

The propyl disulfide and tetrahydrofurfuryl disulfide are readily absorbed from the intestine by diffusion and rapidly distributed throughout the body fluids including the CSF fluid. Preliminary work suggests that they provide metabolically active compounds (Thomson *et al*., 1971; Baker and Frank, 1976) and continual administration of large doses has not been accompanied by any toxicity (Baker and Frank, 1976).

This compound could potentially solve the problem of having to give intramuscular (IM) or IV thiamine to patients being treated in the community. However, no randomized controlled trials have been carried out on patients with WE and it might be unethical to conduct such trials. Although there is an extensive literature on the compound, it is not clear whether the tests required by the US Federal Drug Administration or the Medicines and Healthcare Products Regulatory Agency in the UK have been conducted. It would be especially important to ensure that there is evidence confirming that the metabolism of orally administered thiamine propyl disulfide is identical in brain cells.

PROPHYLAXIS: ADDING THIAMINE TO BEER AND BREAD

Over the past 20 years there have been repeated suggestions that thiamine hydrochloride should be added to beer, and experiments have indicated that this would be acceptable as

far as taste is concerned. This idea is attractive because the more beer an individual drinks the more thiamine he will consume. This, however, raises a number of issues, which have only been partially addressed even by recent advocates (Truswell, 2000; Stacey and Sullivan, 2003). Apart from questions as to whether the thiamine added should be considered a food supplement rather than a drug, and therefore added at low concentrations, one has to ask what message is being sent to the consumer. It would be important to demonstrate that individuals at risk of developing WE would benefit from this suggested strategy. As previously discussed, the amount of thiamine that would be finally absorbed is unknown, since malnutrition alone may cause severe malabsorption of thiamine hydrochloride, and the effects of alcohol on absorption are variable, with certain individuals probably adversely affected. The supplement would not correct the frequent accompanying deficits in vitamin B6, niacin, or protein-calorie malnutrition. (Thomson and Cook, 2000).

It is also possible that individuals drinking the supplemented beer, and their doctors, might be led into a false sense of security. Although their thiamine levels may initially be adequate, it is unlikely that this will prevent the neurotoxicity due to the alcohol alone. The action of alcohol on the N-methyl-D-aspartate (NMDA) receptor at the glutamate site leads to an upregulation of glutamate receptors and increases the vulnerability of the individual to the effects of thiamine deficiency. As the supply of brain thiamine falls (increasing brain glutamate) either because of alcohol-induced malabsorption of thiamine, or any of the other causes of reduced thiamine supply, the individual may experience subclinical episodes of recurrent brain damage. Further studies are required before supplementation of alcoholic drinks with thiamine are either adopted or discarded.

Studies by Harper *et al*. (1998) indicate that there has been a significant reduction in the prevalence of Wernicke-Korsakoff Syndrome (WKS) in Australia in the last 25 years (Table 3). This observation is based on a survey of the brains of deceased people (age >15 years) derived from 2212 sequential autopsies from the New South Wales Institute of Forensic Medicine in Sydney during 1996–1997. Twenty-five cases were diagnosed as WKS (mean age 55 years; 95% male) giving a prevalence of 1.1%, compared with 4.7% found in a similar study conducted in Western Australia between 1973 and 1981 (Harper, 1983). In the recent study only four cases (16%) had been diagnosed during life. Information available indicated that 5.9% of the 2212 brains studied were from people with a 'history which suggested an alcohol problem' giving a prevalence of WKS in alcohol misusers of 19%. Almost half of the 25 WKS patients had been 'treated with thiamine in hospital', although the dose and route of administration was not stated and it was clearly inadequate in preventing/treating the acute brain damage occurring at the time. It was concluded that the observed reduction in the prevalence of WKS may have been due to a genuine reduction in the acute cases. It was suggested that a general improvement in health of patients who had WKS allowed some patients to live longer and to present at a later date with a more chronic brain lesion and that there had been an improvement in the health of the general population in Australia, which may have reduced the number of cases of WE, together with increased awareness of the problem of thiamine deficiency among health professionals. It was also suggested that the declining prevalence might be due to the supplementation of bread in Australia since 1991 with thiamine mononitrate, which is absorbed from the intestine in an identical manner to thiamine hydrochloride (Truswell, 2000; Harper *et al*., 1998). It should be stated that, although there has been a decrease in the prevalence of WKS in Australia, the rate is still higher than in most Western countries (Harper *et al*., 1995). However, other factors must be operating since bread has been supplemented with thiamine in the UK since the 1940s, in the USA since 1930s, (Thomson, 2000) and recently there has been a rise in the incidence of KP in the East End of Glasgow (adult population 160 000). A retrospective analysis of all admissions between 1990 and 1995 showed a rise in the incidence from 12.5 per million in 1990 to 81.25 per million in 1995 (Ramayya and Jauhar, 1997; Cook *et al* 1998). Other changes have occurred during the last 25 years that may be relevant. There has been a dramatic decrease in the number of PMs carried out in hospital in the Western world and most pathology departments still do not perform the careful studies required to identify WE lesions in the brain so that we do not know the true prevalence of WE in different countries. In addition, there has been a change in the total per capita alcohol consumption in Australia, a change in the pattern of drinking, and an increase in the number of alcohol treatment centres. There have also been significant changes in immigration policy in Australia that will alter the gene pool of the population and perhaps its susceptibility to developing WE. It would be reassuring to think that a decline in the incidence of WE might be due to the supplementation of bread with thiamine or to the use of more prophylactic thiamine treatment by general practitioners in patients at risk. However, many cases of WE fail to be diagnosed clinically (84% in the recent study) or at PM in most hospitals, and it would be wrong to make an assumption about the true prevalence based on inadequate evidence.

WE like other neurodegenerative diseases probably results from a combination of thiamine deficiency, excessive alcohol intake, and genetic susceptibility due to a number of different genetic variants (Guerrini *et al*., 2004). If this is the case, then the patients with the greatest genetic susceptibility are likely to develop WE earlier in the natural history of the condition, while other individuals will only be affected when the supply of thiamine to their brain cells reaches a level that is critical for them. (Fig. 1).

It must be remembered that most patients have multiple vitamin deficiencies (Cook *et al*., 1998) and that in some cases of WE, replacement of other vitamins (e.g. folate/B12) may be necessary before clinical response is achieved (Cole *et al*., 1969). Much remains to be understood about the effects of vitamin deficiency on gene expression. Preliminary observations suggest that thiamine may be involved in controlling protein expression for thiamine-dependent enzymes and the thiamine transporter molecule and that this control could be on gene expression rather than on the protein production chain or on the protein assembly pathway. This emphasizes the need for vigilance in the management of all patients with known or suspected alcohol problems and the importance of correcting all defects that are present, under supervision, while maintaining a good diet (Bonner *et al*., 2004). This may be particularly pertinent in the case of

Table 3. Prevention and treatment of WKS in the community

1. Problem

WKS is not rare and occurs in between 1 in 8 and 1 in 3 chronic alcohol misusers, most commonly in those who have a poor diet. It is a lethal form of brain damage, if treated inappropriately, in 20% of cases. In addition, 85% of survivors develop KP, characterized by irreversible short-term memory loss, and in 25% of these patients there is a need for long-term institutionalization

Most alcohol-dependent patients (ICD F10.24, F10.25 or F10.26) and patients engaging in harmful use of alcohol (ICD F10.1), who present to community teams in crisis, will display signs of acute intoxication (ICD F 10.0). The common signs of WKS—confusion, ataxia and coma—are difficult or impossible to differentiate from drunkenness. The eye signs (ophthalmoplegia/nystagmus) are present in only 29% of cases and the most common sign, acute confusion, is non-specific, and may be thought to be caused by intoxication or sobering up

2. Aim

To identify patients at risk of WKS so that hospital admission can be arranged if necessary, or to provide adequate prophylaxis when indicated, by the administration of parenteral/oral B complex vitamins, improved nutrition, and experienced supervision

3. Patient selection

Diagnosis: WE is a clinical diagnosis (Thomson *et al*., 2002). There is no specific routine laboratory test available and no characteristic diagnostic abnormalities in the CSF, electroencephalograph or evoked potentials. A brain MRI rarely shows changes in the tissue indicating WKS

4. Patients who should NOT be treated in the community

Delirium tremens or a history of delirium tremens

Patient diagnosed with WE or in whom a presumptive diagnosis of WE should be made, that is when there is a history of alcohol misuse with one or more of the following unexplained symptoms

- Ophthalmoplegia
- Ataxia (not due to intoxication)
- Acute confusion (not due to intoxication)
- Memory disturbance
- Comatose/unconscious
- Unexplained hypotension & hypothermia

Severe alcohol dependence

History of seizures

Severe concurrent physical or mental illness (including cognitive impairment)

Repeated unsuccessful attempts at detoxification

5. Patients in community who remain at risk of WE

Patients undergoing community detoxification

- Because they refused inpatient admission
- For whom inpatient care was indicated but was not available
- Who develop hypotension and hypothermia
- Who refuse parenteral vitamin therapy; where possible these patients should be asked to confirm their refusal in writing (waiver). A proportion of such patients will be unable to give 'informed consent' to refuse, thus causing an ethical/legal dilemma that needs to be addressed

Patients who develop unrecognized WE who could be protected with adequate prophylaxis

6. Other causes of WE which may co-exist with alcohol misuse causing patients to be at additional risk

Protein-calorie malnutrition from malabsorption or forced/self-imposed inadequate diet, anorexia nervosa

Patients with protracted vomiting including pregnancy, toxaemia

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

Hyperalimentation, AIDS, drug misuse

Patients on diuretics for ascites

Partial gastrectomy, gastrectomy or gastric stapling, gastric or oesophageal carcinoma. Cancers that have spread throughout the body

Pernicious anaemia

Prisoners admitted to police cells, prison, individuals living in hostels, itinerants

Patients with Alzheimer's disease or neglect in old age, especially if living alone

Chronic Schizophrenia

Widespread tuberculosis

Thyrotoxicosis (very high thyroid hormone levels)

Conditions resulting in increased requirements: fever, pregnancy, breastfeeding, and adolescent growth

Malaria

Anti-thiamine factors (ATFs). Certain plants contain ATFs that react with thiamine to render it inactive, e.g. consuming large quantities of tea or coffee

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

7. Complications of persistent alcohol misuse: secondary thiamine deficiency

Thiamine malabsorption due to malnutrition and/or alcohol misuse

Hepatic disease reduces storage and interferes with thiamine metabolism

Alcohol accelerates cerebellar metabolism, inhibits thiamine pyrophosphokinase and renal tubular reabsorption

Magnesium required as a co-factor

Impaired utilization of thiamine and neurotoxicity

Alcohol increases nutrient requirements

8. Treating patients at risk

Oral thiamine hydrochloride cannot be relied upon to treat patients at risk of WE. There is also a serious problem with compliance

Consider magnesium deficiency and other vitamin deficiencies e.g. niacin, vitamin B6, folate, and vitamin B12 etc

Patients at risk should receive one pair of IM high potency B-complex vitamins (Pabrinex) o.d. for a minimum of 3–5 days

We recommend that administration is recorded in the GP record in the same way as immunizations are recorded. Ideally patients should be given a card with the dose/duration of treatment recorded on it. However, individuals with alcohol misuse are notoriously unreliable, so it would seem sensible to keep central records or pass the information to a family member, next of kin, primary care trust, or community pharmacist. Thus we are recommending a record of parenteral thiamine administration and adverse reactions

IM Pabrinex contains 500 mg ascorbic acid, 160 mg nicotinamide, 50 mg pyridoxine hydrochloride, 4 mg riboflavin, 250 mg thiamine hydrochloride/7 ml

Table 3. Continued

It should be noted that anaphylactoid responses can occasionally occur when B vitamins are given orally, IV, IM, or SC. These are most often seen after multiple administrations when given IV as a bolus, instead of a slow infusion over 30 min (Thomson *et al*., 2002). The risk of anaphylactoid reactions has probably been overstated for IM preparations. A history of asthma and atopy and other allergies should be obtained, including a history of other drug allergies
9. Treatment to be administered by
GP or trained nurse at practice or at patient's home
Trained nurse/GP should
(a) Be 'in date' for basic life support training
(b) Carry mini-jet preparation of 0.5 ml adrenaline, 1:1000 solution
(c) Should remain with the patient for at least 15–20 min after the injection

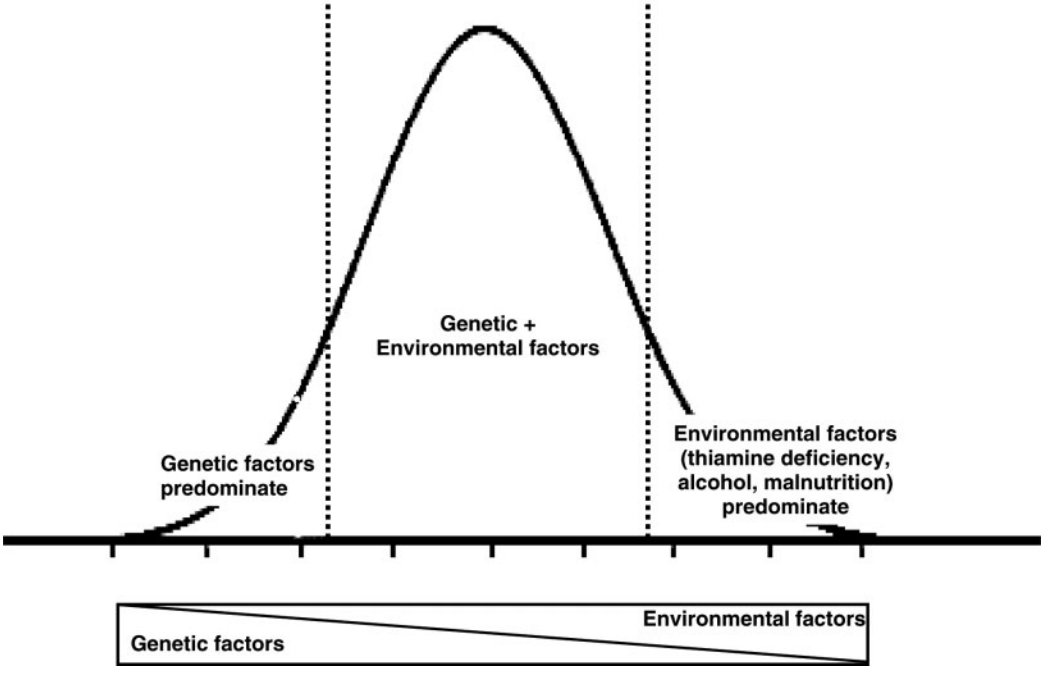

Fig. 1. Interaction between genetic and environmental factors in the pathogenesis of Wernicke's encephalopathy. The diagram represents a theoretical population of patients with WE. The patient on the left-hand side have a putative genetic loading and are possibly at increased risk of developing WE than patients on the right-hand side in whom environmental risk factors predominate.

alcohol-dependent patients who are at risk of alcohol withdrawal, as withdrawal in itself increases the requirement for thiamine, at a time when these malnourished patients have a very compromised nutritional intake. Alcohol-dependent individuals have been shown to demonstrate a decreased ability to filter information during the first 7 days of an alcohol withdrawal episode (Keedwell *et al*., 2001) and this effect was more marked in those with a history of delirium tremens. The role of thiamine in this process is not known but merits further investigation.

TREATING THE PATIENTS AT RISK

Oral thiamine hydrochloride cannot be relied upon to supply adequate thiamine replacement for patients at risk (Thomson, 2000), and thiamine propyl disulfide is not available except as a nutritional supplement at present. There is also the serious problem of lack of compliance in this group of patients with oral preparations and, therefore, the logical choice is between IV or IM thiamine therapy, the only parenteral high-potency B-complex vitamin therapy licensed in the UK being Pabrinex. Ampoules no. 1 and no. 2 contain: Vitamin B1 (thiamine) 250 mg; Vitamin B2 (riboflavin) 4 mg; Vitamin B6 (pyridoxine) 50 mg; nicotinamide 160 mg; and Vitamin C 500 mg. (Link Pharmaceuticals Ltd). Although IV thiamine given in 100 ml of saline over 30 min remains the route of choice for patients in whom a presumptive diagnosis of WE has been made, or for patients in whom the diagnosis is beyond doubt, the use of IM thiamine hydrochloride for 'at-risk' patients in the community has many advantages (Cook *et al*., 1998). The Scottish Intercollegiate Guidelines Network (SIGN) recently suggested that 'at-risk' patients 'detoxifying in the community should be given IM Pabrinex (one pair of ampoules daily for 3 days)' (SIGN, 2003). This could be administered in a number of locations, including the GP surgery, the accident and emergency department, outpatient clinic, or day hospital, provided facilities for treatment of anaphylactoid reactions are available, 'such as any setting where routine immunizations are given'. Intramuscular Pabrinex has a lower incidence of anaphylactoid reactions than the IV preparation, at 1 per 5 million pairs

of Pabrinex ampoules, which is far lower than many frequently used drugs that carry no special warning in the BNF. Indeed the SIGN document noted that there had been only one case of anaphylaxis solely attributable to IM Pabrinex since it was introduced in 1996. For further discussion of these points the reader is referred to Thomson *et al*., 2002.

Other considerations include:

(i) IM Pabrinex causes some discomfort even though it contains a local anaesthetic, but we believe that this is insignificant in comparison with the potential benefits and reduced risk of adverse reactions.

(ii) In the unlikely event that the patient develops an anaphylactoid reaction, the IV preparation given by slow infusion can be stopped, but once the IM drug has been given, elimination would depend on excretion that would take some hours.

(iii) As shown in Fig. 2, following the administration of 200 mg of thiamine IV the concentration of thiamine in the serum is initially much higher than after the IM route favouring transport into the brain by diffusion. However, after ~20 min, the serum level falls below that following IM thiamine. Thiamine by IV infusion over 30 min is likely to produce a lower concentration than the IV bolus dose but this would be relatively constant during the period of infusion.

(iv) A study to compare the efficacy of treating WE by all three methods would require large numbers of subjects with similar initial pathological involvement and a careful assessment of recovery. Confounding factors leading to a variable clinical response to treatment include:

(1) Varying degrees of permanent brain damage at the time of presentation;
(2) Different rates of regeneration of nervous tissue;
(3) The duration of the process of withdrawal from alcohol;
(4) The presence of multiple nutrient deficits, e.g. magnesium required for thiamine dependent enzymes.
(5) The effect of recurrent subclinical episodes of WE increasing the severity of the presenting signs and symptoms;
(6) Accompanying brain damage of known (e.g. road traffic accidents (RTA), head injury) or unknown aetiology e.g. Alzheimer's disease, encephalitis, etc. It is possible that many patients with Alzheimer's disease may also have KP since these patients are at risk of thiamine deficiency and confusion that may be the only sign likely to be attributed to the Alzheimer disease.
(7) Age of the patient.

Ambrose *et al*. (2001) have conducted a randomized double blind multi-dose study into the therapeutic benefits of thiamine in an alcohol-dependent at-risk group of patients without overt WE. Based on the response of their mental state, the results suggested that an IM dose of ⩾200 mg daily may be required to show improvement in such patients (Ambrose *et al*., 2001; Thomson *et al*., 2002). Further studies with adequate psychological testing are required with long-term follow-up (1–2 years) to determine the optimum size of the prophylactic dose of thiamine.

At present it is suggested that patients at risk in the community should receive:

- One pair of IM high potency B-complex vitamins (Pabrinex) 250 mg of thiamine once daily for 3–5 days.
- It should be given by a GP or a trained nurse at the practice or in the patient's home.
- The trained nurse should be 'in date' for basic life support training.

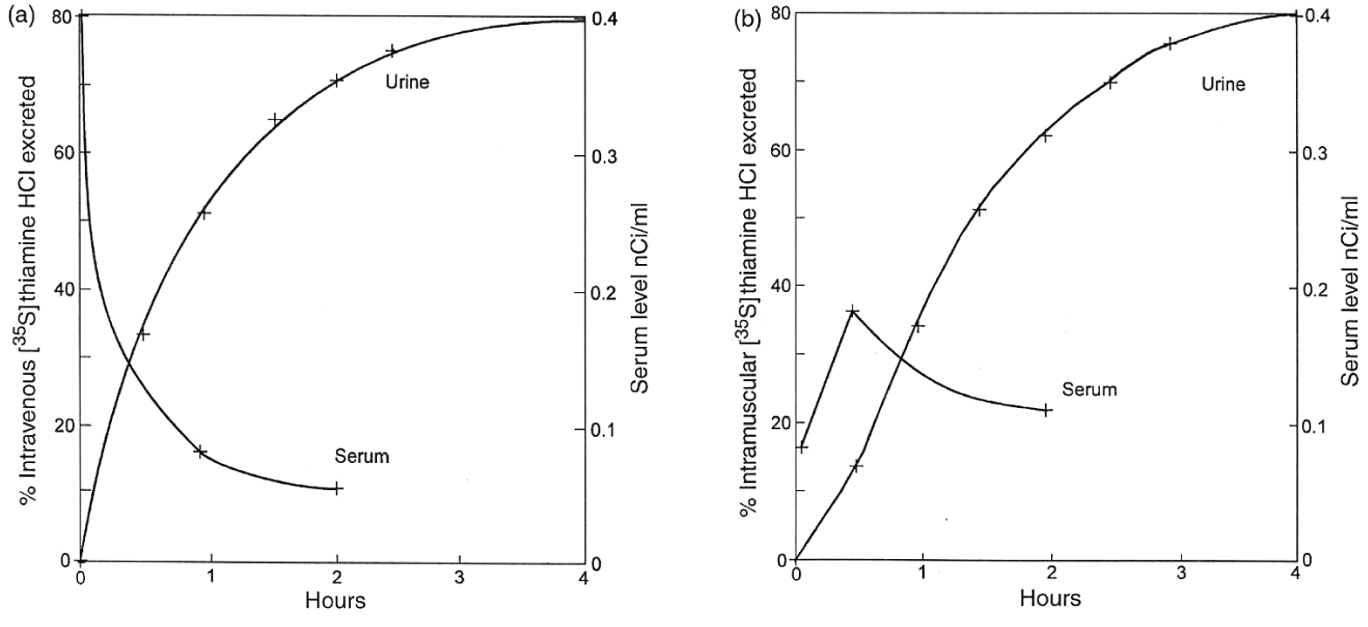

Fig. 2. Radioactivity in serum and urine after (a) IV administration, (b) IM administration of a 200 mg dose of (35S) thiamine hydrochloride. (Thomson, 2000; with permission).

- The GP/Nurse should have with them a mini-jet preparation of 0.5 ml adrenaline 1:1000 solution (500 μg). This will often be carried by patients known to be allergic to such things as bee or wasp stings.
- The nurse should remain with the patient for 15–30 min after the injection to ensure that there are no untoward effects.
- Should the patient require further treatment, then they should be transported urgently to a hospital emergency department without delay.

CONCLUSIONS AND COMMENTS

PM findings on patients dying in hospital indicate that we are failing to diagnose up to 90% of patients with WE. It is difficult to know how frequently this occurs in the community where often less experienced personnel are responsible for treatment services. A long history of excessive alcohol use, together with a poor diet, predisposes the individual to brain damage, by initiating a series of detrimental metabolic and structural changes, which severely limit the supply of thiamine to brain cells, at a time when the requirements of many tissues are increased: these patients are therefore at risk. If preventable brain damage is to be avoided, all members of the staff responsible for the care of the patient must receive adequate training in identifying the individuals who are at high risk of developing WE. The natural history of WE that may help to identify patients whose thiamine levels are reduced to a critically low level at an earlier stage of depletion has been discussed in another paper (Thomson and Marshall, 2005). It is important to remember that a number of factors, including inhibition of thiamine absorption, cirrhosis, and diuretics will also contribute to thiamine malnutrition.

It is necessary to ensure that such vulnerable people can be given the appropriate prophylactic treatment and that a presumptive diagnosis of WE is made where appropriate, to allow transfer to hospital for further treatment (Cook *et al*., 1998; Thomson *et al*., 2002). We have reviewed the indications for treatment. It is recommended that patients at risk of developing WE should be given 250 mg of thiamine (Pabrinex) IM daily for 3–5 days. The incidence of anaphylactoid reactions is very low and the injection may be given by an appropriately trained nurse or a GP. The requirements for inpatient care have been reviewed elsewhere (Cook *et al*., 1998; Thomson *et al*., 2002). Further work is required to monitor the results of treatment in the community and to define more clearly the group of patients who require parenteral vitamins because of induced malabsorption. Adequate and prompt treatment has many advantages both for the individual and for society in terms of reduced expenditure, the patient's increased working life, and preservation of their skills. Early intervention may also limit neurotoxicity from the combined effects of thiamine depletion and ethanol metabolism. Initially, the damage to the protein receptors can be ameliorated by providing a higher concentration of brain thiamine, but ultimately there may come a point at which thiamine will not correct the problem, and in this situation the degree of neurotoxicity is likely to determine the degree of recovery from brain damage. Over 25 years ago, it was calculated that an estimated annual institutionalization rate of eight patients with WE per million of the adult US population would cost $70 million per year (Centerwall and Criqui, 1978). The human cost is incalculable.

Acknowledgements — The authors would like to thank Dr Roger Bloor for his constructive criticism and helpful suggestions and Dr Jonathan Chick for his editorial guidance. The authors are also thankful to Professor Robin Touquet, Department of Accident and Emergency Medicine, St Mary's Hospital, Praed Street, London W2 1NY, for his advice on the immediate management of anaphylaxis as a result of treatment with IM Pabrinex.

Dr Allan D. Thomson: Disclaimer

I received payment and expenses from Link Pharmaceuticals (manufactures of Pabrinex) in respect to lectures and consultancy some years ago. Link Pharmaceuticals have also assisted with the process of literature searching and undertaking a survey on the use of Pabrinex in 1998 in conjunction with Professor C. C. H. Cook. More recently, Link Pharmaceuticals have contributed on one occasion towards the cost of an airfare to attend a conference where I was giving an invited unpaid international lecture on Wernicke's Encephalopathy.

Dr E. Jane Marshall: Disclaimer

I received payment and expenses from Link Pharmaceuticals (manufacturers of Pabrinex) in respect to lectures some years ago.

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