Alcohol & Alcoholism Vol. 37, No. 6, pp. 513–521, 2002

INVITED SPECIAL ARTICLE

THE ROYAL COLLEGE OF PHYSICIANS REPORT ON ALCOHOL: GUIDELINES FOR MANAGING WERNICKE'S ENCEPHALOPATHY IN THE ACCIDENT AND EMERGENCY DEPARTMENT

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(*Received* 7 *February* 2002; *in revised form* 1 *May* 2002)

Abstract — The Royal College of Physicians (London) recently published its latest report on alcohol misuse entitled 'Alcohol — Can the NHS Afford It?'. Part of this document, encompassing our views, has made specific recommendations for the management of patients in the Accident and Emergency (A&E) Department who may possibly have, or are at risk of developing, Wernicke's encephalopathy. Patients showing evidence of chronic alcohol misuse and suspected of having a poor diet should be treated at the outset with B vitamins intravenously or intramuscularly, especially when the clinical signs are initially masked by drunkenness at presentation to the A&E Department. This commentary offers a review of the scientific foundations on which these recommendations have been made.

INTRODUCTION

In February 2001 the Royal College of Physicians (London) published its latest report entitled 'Alcohol — can the NHS afford it?' (Royal College of Physicians, 2001). This report deals with the burden that alcohol misuse places on the general hospital services in the UK and how this might be managed or reduced. Previous reports have included 'Alcohol — a great and growing evil' (Royal College of Physicians, 1987), 'Alcohol and the young' (Royal College of Physicians and British Paediatric Association, 1995) and 'Alcohol and the heart in perspective; sensible limits reaffirmed' (Royal College of Physicians, Royal College of Psychiatrists and Royal College of General Practitioners, 1995). This latest report (Royal College of Physicians, 2001) makes wide-ranging suggestions for auditing and improving the services provided for people with alcohol problems. It also contains recommendations for the prevention and treatment of Wernicke's encephalopathy (WE) in the Accident and Emergency (A&E) Department (Appendix III of that report: see Table 1 of this article). We wish here to deal with a specific area of alcohol-related disease, that of the recognition, prevention and treatment of WE in the acute hospital setting. It needs to be dealt with in detail, because of lack of knowledge among the medical profession, scanty literature and misinformation concerning prevention and treatment. WE is the acute phase of a relatively common and potentially lethal condition resulting from thiamine (vitamin B_1) deficiency. Failure to treat WE adequately leads to a chronic form of the disease (Korsakoff psychosis, KP) characterized by severe short-term memory loss. Because of the close relationship between WE and KP, reference is often made to the Wernicke–Korsakoff syndrome (WKS) as if it were a single entity.

For many years, WE was treated by giving intravenous (i.v.) Parentrovite (later Pabrinex) in the UK and i.v. thiamine hydrochloride in some other countries, notably the USA. During the mid-1990s it became apparent to us (C.C.H.C. and A.D.T.) that many doctors in the UK had stopped using i.v. therapy, even in some patients believed to have WE, and had substituted oral thiamine. This prompted us to review the current state of knowledge (Cook *et al*., 1998) and to conduct a survey of A&E medicine specialists, psychiatrists and others involved in treating alcoholic patients. The results of this enquiry indicated that many doctors were confused about the correct therapy and that WE was more common than previously suspected (Hope *et al*., 1999). For this reason we have developed protocols (see Tables 1 and 2), which it is hoped will aid doctors in different disciplines to be vigilant and to institute appropriate treatment for their patients as early as possible, particularly in the A&E Department, where most cases present.

THE DISEASE SPECTRUM

Wernicke's encephalopathy is an acute neuropsychiatric condition due to an initially reversible biochemical brain lesion caused by overwhelming metabolic demands on cells which have depleted intracellular thiamine (vitamin B_1). In the UK, it is most commonly seen in chronic alcohol misusers, and if inadequately treated with thiamine (given by the wrong route, in too small a dose or too late), leads to irreversible structural changes producing loss of short-term memory and an impaired ability to acquire new information. Victor *et al*. (1989), in their innovative and comprehensive studies in Boston (USA), found that only 16% of WE patients treated with inappropriately low parenteral doses of 50–100 mg of thiamine daily recovered fully, with a reported death rate of 17–20%, and 84% developed KP. Only 21% of these patients with KP showed complete recovery; 26% showed no improvement, 28% only slight improvement and 25% showed significant recovery from the amnesic state which may take from 2 months to 10 years. Twenty-five per cent of patients with KP require

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Table 1. Prevention and treatment of Wernicke's encephalopathy (WE) in the Accident & Emergency (A&E) department

1. The problem:
WE (also known as Wernicke–Korsakoff syndrome) is a relatively common and potentially lethal condition resulting from thiamine deficiency, but is preventable or reversible if treated early. Established WE can have major long-term consequences, with patients requiring permanent institutional care. It is commonest in heavy drinkers who have a poor diet. Such patients may be unpopular with staff if unkempt, drunk or abusive.
Most alcohol-dependent patients presenting to A&E will spontaneously leave on sobering up. The common signs of WE — confusion, ataxia and varying levels of impaired consciousness — are difficult or impossible to differentiate from drunkenness. The eye signs (ophthalmoplegia/nystagmus) are present in <30% of cases. Because of this, WE may go unrecognized if not considered, e.g. in the affluent or elderly.
Heavy drinkers presenting to A&E — often collapsed and/or with a head injury — require repeated neurological assessment. The intoxicated patient who does not recover fully and spontaneously may be suffering from WE. Only if such a patient is admitted will full assessment be possible and further treatment be practical. There is no simple blood test to determine patients at risk of WE.

2. The need:
To prevent the development of, and to treat symptoms of, WE by administration of parenteral B complex vitamins.

3. Treatment:
The only available intravenous (i.v.) treatment which includes thiamine (B_1), riboflavin (B_2), pyridoxine (B_6), and nicotinamide is Pabrinex (Parentrovite was discontinued in 1993). The intramuscular (i.m.) Pabrinex preparation includes benzyl alcohol as a local anaesthetic.
Two pairs of vials of Pabrinex 1 and 2 diluted in 100 ml of crystalloid should be given i.v. over 30 min, initially in A&E (see 4). If the patient is admitted, consider two pairs of vials three times daily for 2 days i.v. to be followed, if any improvement, by one pair per day for 5 days (i.v. or i.m.) at the discretion of the admitting team.

4. Who to treat:
All patients with any evidence of chronic alcohol misuse and any of the following: acute confusion, decreased conscious level, ataxia, ophthalmoplegia, memory disturbance, hypothermia with hypotension, when initially seen in A&E may well be drunk but still treat (see 3). Patients with delirium tremens may often also have WE. All of these patients should be presumed to have WE and be considered for admission.
All hypoglycaemic patients (who are treated with i.v. glucose) with evidence of chronic alcohol ingestion must be given i.v. Pabrinex immediately because of the risk of acutely precipitating WE.

long-term institutionalization (Cook *et al*., 1998). Thiamine must therefore be given as soon as possible in adequate amounts to all patients with diagnosed or incipient WE and by a route that ensures sufficient supply of thiamine especially to the dependent enzymes in brain cells.

It is also well recognized that all hypoglycaemic patients — whether or not attributable to chronic alcohol misuse — who are treated with i.v. glucose must be given i.v. thiamine at the same time to avoid the risk of precipitating WE.

THE EVIDENCE FOR AN UNRECOGNIZED PROBLEM

WE is difficult to diagnose because the classic triad of signs (confusion, ataxia and ophthalmoplegia) occurs in only 10% of cases, and drunk patients are often both confused and ataxic. Other clinical signs such as acute mental impairment, obtundation, pre-coma and coma occur in 82% of patients with WE, which may easily be attributed to intoxication, alcohol withdrawal or to concurrent morbidity such as head injury. Ataxia occurs in only 23% of patients and ophthalmoplegia in only 29% (Harper *et al*., 1986).

The patients studied by Victor *et al*. (1989) were often grossly malnourished and it would be reasonable to anticipate that, if patients are treated adequately before all of the classic signs of WE have been allowed to develop, much irreversible brain damage can be prevented. In Victor *et al*.'s (1989) report, death occurred in 17% of patients in the early stages of the illness (1–21 days after onset, average: 8 days). Death was usually attributed to accompanying conditions such as bronchopneumonia, tuberculosis, pancreatitis and bacterial meningitis as the primary or secondary causes. However, the authors concluded that 'it is logical to assume … that the brain stem lesions and the general nutritional depletion contributed to the patient's death, but the extent to which they contributed could not be quantified'.

Information gained from post-mortem studies demonstrated the characteristic lesions of WE in ~1.5% of patients representative of the general population and 12.5% of alcohol misusers coming to post-mortem (Harper *et al*., 1986, 1995; Cook *et al*., 1998). This latter figure is increased to 30% if patients with cerebellar damage as a result of thiamine deficiency are included (Torvik *et al*., 1982). Only 5–14% of patients with WE are diagnosed in life (Torvik *et al*., 1982; Blansjaar and Van Dijk, 1992) and only 18% of patients with KP had previously been diagnosed as having WE. Since only 10% of patients present with the classical triad of signs, we may be failing to make the diagnosis of WE in up to 90% of patients (Fig. 1).

WHO IS MOST AT RISK?

Specifically in A&E Departments, the drunk of no fixed abode, who may be unkempt and smelly, risks having his/her signs of confusion and ataxia put down to alcohol intoxication. The A&E notes of such patients are often put to the back of the queue. On waking up, often still with high levels of alcohol, the patient spontaneously leaves, without having been assessed by a doctor and without any treatment with B vitamins. It is only if he/she can be retained until completely sober — something that is often impractical — that a possible diagnosis of WE can be made.

Families may reject their drunk relative in life, only to litigate in death, partly to exorcise the guilt that they feel for their prior rejection (Touquet *et al*., 2000). Treating the chronic alcohol misuser of 'no fixed abode' with B vitamins in A&E may perhaps prevent such patients being institutionalized at high cost to society when their incipient KP has become a severe disability of intermediate or longer duration. In addition, the A&E doctor, knowing that there is a treatment regime for the previously rejected patient, may more readily

Table 2. Diagnosis and treatment summary for in-patients

Diagnosis:
WE is a clinical diagnosis (see Table 1): there is no specific routine laboratory test available and no characteristic diagnostic abnormalities in cerebrospinal fluid, brain imaging, electroencephalograph or evoked potentials.
Causes:
- Chronic alcohol misuse
- Protein-calorie malnutrition from malabsorption or forced/self imposed inadequate diet
- Patients with protracted vomiting
- Carbohydrate loading i.v./oral when thiamine stores are minimal
- Chronic renal failure
- Hyperalimentation, AIDS, drug misuse
- Genetic abnormality of transketolase enzyme

Thiamine replacement must be given immediately in adequate amounts parenterally to avoid irreversible brain damage. Consider also magnesium, vitamin B_6 and nicotinic acid deficiencies.
Oral thiamine is poorly absorbed and ineffective in both prophylaxis and treatment of WE.
High-risk patients:
- Detoxification
  - (a) In-patient: planned or occurring during treatment of other medical/surgical conditions
  - (b) Community: when no hospital bed is available but would have been indicated or patient refuses admission or complications develop
- Alcohol misuse with ophthalmoplegia, ataxia, acute confusion, memory disturbance, unexplained hypotension or hypothermia
- Road traffic accident head injuries
- Poorly nourished patients and all alcoholic patients should be given Pabrinex before i.v. glucose, even in absence of signs, since this may precipitate WE
- Consider other causes as listed above
- Significant weight loss, poor diet, signs of malnutrition

Treatment regime for WE:
- Objective: to replenish vitamin stores and optimize metabolic balance. Adults also require magnesium 10–30 mEq, potassium 60–180 mEq and phosphate 10–40 mmol/l daily.
- Drug name: Pabrinex is the only parenteral high potency B-complex vitamin therapy licensed in UK.
- Ampoules no. 1 and no. 2 contain:

Vitamin B_1 (thiamine)	250 mg
Vitamin B_2 (riboflavin)	4 mg
Vitamin B_6 (pyridoxine)	50 mg
Nicotinamide	160 mg
Vitamin C (ascorbic acid)	500 mg

- Parenteral B vitamins given in 100 ml normal saline over 30 min very rarely causes adverse reactions but appropriate resuscitation facilities must be available.
  - (a) Prophylaxis WE (patients at risk). One pair of vitamins B + C (Pabrinex i.v.) by i.v. infusion once daily for 3–5 days[a]
  - (b) Established or presumptive diagnosis of WE
- Two pairs i.v. high potency parenteral B-complex vitamins (Pabrinex) three times daily for 3 days
  - (a) No response — discontinue
  - (b) Response — one pair i.v. or i.m. ampoules once daily for 5 days or until clinical improvement ceases
- Magnesium: Co-factor required for normal functioning of thiamine-dependent enzymes and neurochemical transmission. Stores are usually inadequate in chronic alcohol misusers and malnourished patients. Do not administer i.v. magnesium unless hypomagnesaemia is confirmed.
- Adult dose: 35–50 mmol of magnesium sulphate added to 1 litre isotonic (saline) given over 12–24 h. Dose to be titrated against plasma magnesium levels. Reduce dose in renal failure.
- Contraindicated: in patients with documented hypersensitivity and those with heart block, Addison's disease, myocardial damage, severe hepatitis or hypophosphataemia.

[a]See Appendix 2, Royal College of Physicians (2001).

see them rather than simply relegating their notes to the back of the pile.

Patients who show evidence of WE at post-mortem have less brain mass. Therefore, in life the subdural space is larger and often, in addition, clotting time is prolonged from liver dysfunction due to alcohol misuse. Therefore they are at greater risk of developing subdural haematoma secondary to head injuries. The initial signs of a developing intracranial bleed may be masked by drunkenness. Hence the added importance of an expeditious assessment in A&E, for consideration for a computed tomography scan and review by an anaesthetist.

THIAMINE DEPRIVATION AND BRAIN DAMAGE

Many factors interact to reduce intracellular thiamine in brain cells. As the deficiency develops, enzymes and systems dependent upon thiamine will begin to function less well, leading eventually to cell death (Fig. 2). These include the thiamine-dependent enzyme transketolase involved in the pentose phosphate pathway, the maintenance of myelin sheaths in the nervous system, lipid and glucose metabolism and branched chain amino acid production. Thiamine deficiency also reduces the conversion of pyruvate to acetyl co-enzyme A. This increases lactic acid production, and the accompanying pH change may damage the apo-enzyme, making it less efficient (Butterworth, 1989; Todd *et al*., 1999). Thiamine is also a co-factor for the conversion of α-ketoglutarate to succinate. The citric acid cycle may, however, continue by by-passing the step though glutamate and GABA metabolism which can constitute 10% of citric acid cycle activity (Baxter, 1976; Butterworth, 1989; McEntee, 1997; Todd *et al*., 1999). Patients are frequently deficient in several vitamins, and both vitamin B_6 and riboflavin (vitamin B_2) are co-factors in the conversion

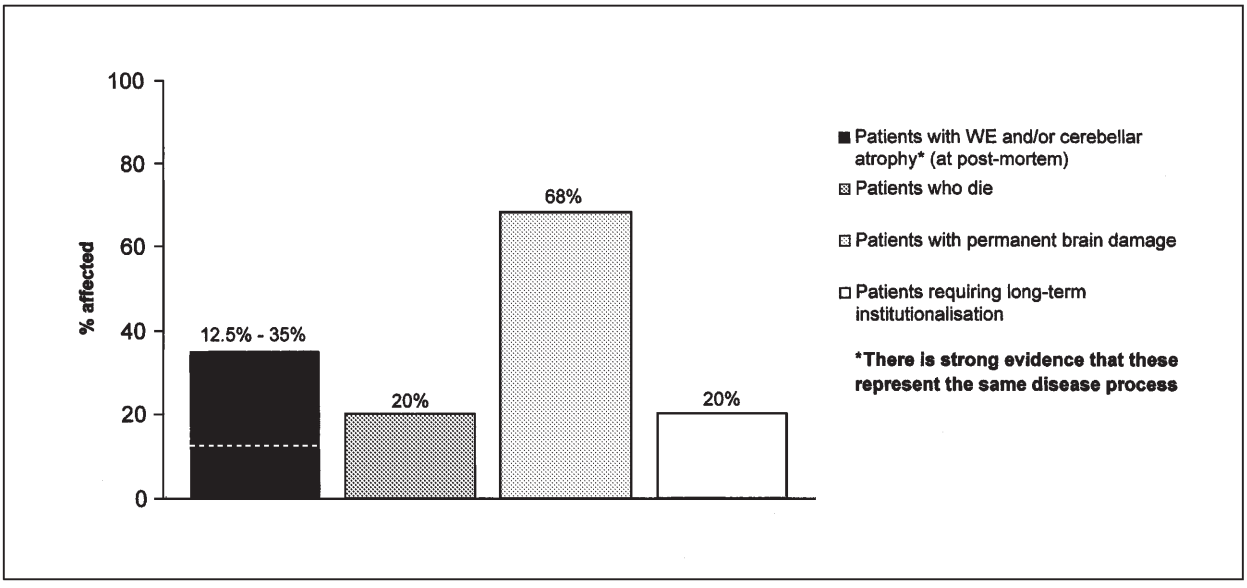

Fig. 1. Mortality and morbidity of patients inadequately treated for Wernicke's encephalopathy (WE).

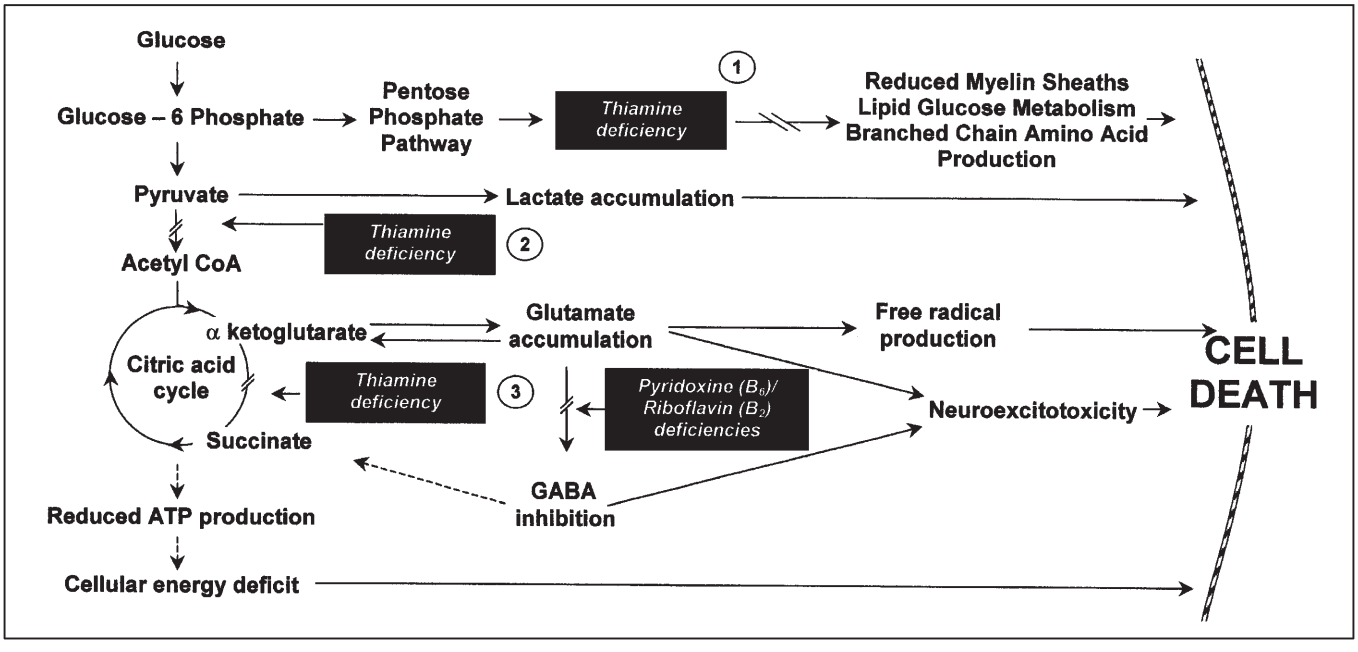

Fig. 2. Potential mechanisms leading to brain damage.
Thiamine-dependent enzymes: (1) transketolase; (2) pyruvate dehydrogenase complex; (3) α-ketoglutarate dehydrogenase complex.

of glutamate to GABA (Ryle and Thomson, 1984). Glutamate accumulation may increase free radical production (Todd *et al*., 1999). Vitamin B deficiencies will affect the efficacy of the citric acid cycle and result in a cellular energy deficit (Schiff, 1941; Todd *et al*., 1999). Early correction of the 'biochemical lesion' will prevent progression to permanent structural damage and cell death. Vitamin B_1 is the most important and urgently required of the B vitamins.

CAN LABORATORY TESTS HELP MAKE THE DIAGNOSIS?

Until now we have discussed the clinical problem and the biochemical lesion. Because of the biochemical nature of thiamine deficiency, many tests have been developed for measuring thiamine status. Early demonstration by Peters (1936) that pyruvate accumulates in the brain stem of

thiamine-deficient pigeons led to measurement of pyruvate in blood, since pyruvate production increases during thiamine deficiency (see Fig. 2). This was used for many years together with blood lactate measurements to determine the state of thiamine nutrition in man (Peters, 1936). However, these measurements are limited by a lack of specificity and technical difficulty (Victor *et al*., 1989). Although lactate analysers are widely used in clinical laboratories, pyruvate determination presents problems and thus requires special technical precautions not readily available for A&E testing.

In 1964, Baker *et al*. developed a bioassay for measuring thiamine activity in blood, urine and other tissues using the protozoon *Ochromonas danica*, and subsequently high performance chromatography was used to measure blood thiamine levels. The measurement of red blood cell transketolase activity (a thiamine dependent enzyme) also provides a measure of thiamine status.

Although Baker's pioneering work and the use of the other tests have provided us with invaluable information about the extent and importance of thiamine depletion, none of the tests developed so far can be used to 'diagnose' WE. They will identify patients with extremely low circulating levels of thiamine, who are thus at risk of developing WE and KP. However, the tests are not generally available routinely on an emergency basis, and even if they were, it is more important to make a presumptive diagnosis of WE and to treat the patient as soon as possible (Cook *et al*., 1998).

HOW ADEQUATE IS TREATMENT WITH ORAL THIAMINE?

A survey of the current practice of psychiatrists and A&E medicine specialists, who are frequently responsible for treating alcohol misusers, showed that there was no consensus as to which vitamins might be beneficial, nor the best method of administering them (Hope *et al*., 1999). In addition there is disturbing evidence of an increase in the prevalence of KP in the UK (Ramayya and Jauhar, 1997; Smith and Flanigan, 1998). It is entirely reasonable to recommend that well-nourished patients, with no history of dietary neglect, adequate dietary intake and no neuropsychiatric symptoms/signs of WE or peripheral neuropathy be given oral thiamine hydrochloride 100 mg orally three times per day (Morgan and Ritson, 1998). This recommendation assumes that an adequate dietary history or evaluation has been carried out. This group of patients as described are at minimal risk of developing WE, although between 30 and 80% of alcoholic patient populations have low circulating levels of thiamine, depending upon the patient group investigated (Cook *et al*., 1998). It is thus vitally important to identify those patients who are at serious risk of developing WE, but who cannot easily be distinguished clinically.

In healthy subjects, the maximum amount of thiamine which can be absorbed from a single oral dose is ~4.5 mg, since absorption is an active, rate-limited process, the enzymes involved requiring thiamine themselves for their own production. An oral dose of ~30 mg will achieve this figure and no increase in absorption occurs with any larger single dose (Thomson, 2000). The dose of 100 mg orally three times per day would allow ~4.5 mg × 3 = 13.5 mg to be absorbed daily. This would be adequate for healthy subjects or patients with mild deficiency. Thiamine transport in man across the blood–brain barrier, unlike the intestine, occurs by both passive and active mechanisms (Fig. 3), so that rapid correction of brain thiamine deficiency can occur if a steep plasma:central nervous system concentration gradient is established. In chronic alcohol misusers, malnutrition can reduce intestinal thiamine absorption by ~70%, decreasing serum levels from 30 to 98% below the lower level established for normal subjects. Alcohol itself alone can also decrease absorption by 50% in one-third of patients who are not malnourished (Thomson, 2000). Although the investigations could not be performed for ethical reasons in man, it seems reasonable to assume that heavy drinking in the presence of malnutrition will further impair the absorption of thiamine which, in certain individuals, is already reduced to critical levels. The logical conclusion is that correction of WE requires high blood concentrations of thiamine which can only result from parenteral therapy.

Evidence suggests that, in the most vulnerable patients, the total absorption of thiamine from three oral doses of 100 mg each would be reduced to one-third or less of that in healthy subjects, that is ~5 mg in 24 h. The number of studies that have been carried out to establish the size of the malabsorbing group has been limited, but it could be more extensive than expected. Work by Holzbach (1996) indicates impaired thiamine absorption in patients experiencing delirium tremens. It is likely that patients will exhibit varying degrees of absorption depending on the degree of malnutrition and the amount of alcohol being consumed. Until and unless absorption or utilization tests are widely available and performed on more patients with a presumptive or established diagnosis of WE, we will not be sure how safe it is to rely on oral therapy in our most vulnerable patients. In any event, it seems unlikely that the oral route could provide the blood concentrations required in an emergency situation; this includes the ataxic and confused drunk of 'no fixed abode' who may be repeatedly brought to A&E with the presentation of 'collapse'. It has been shown that parenteral thiamine doses of 100 mg daily do not prevent death in all patients, and parenteral doses of up to 1 g may be required in the first 12 h (Nakada and Knight, 1984; Lindberg and Oyler, 1990). It can therefore be seen that the 14 mg of thiamine absorbed from intensive oral therapy in patients without impaired absorption, although adequate to replete mild degrees of deficiency, over time will not be sufficient to treat WE in patients with severe thiamine deficiency who are at immediate risk of developing KP. It would help if a genetic marker could be found to identify susceptible individuals so that they could receive therapy prophylactically in order to prevent the devastating consequences of WE.

SIZE OF PARENTERAL THIAMINE DOSE REQUIRED

The dose of thiamine required to prevent or treat WE in most alcoholic patients is believed to be >500 mg once or twice daily, given parenterally for 3–5 days (Cook *et al*., 1998). This estimate is based on data from uncontrolled trials and from empirical clinical practice. Recently, Ambrose *et al*. (2001) conducted the first randomized double-blind multi-dose study into the therapeutic benefits of thiamine in an alcohol-dependent sample without clinically apparent WE. Based on responses of their mental state, results suggested that

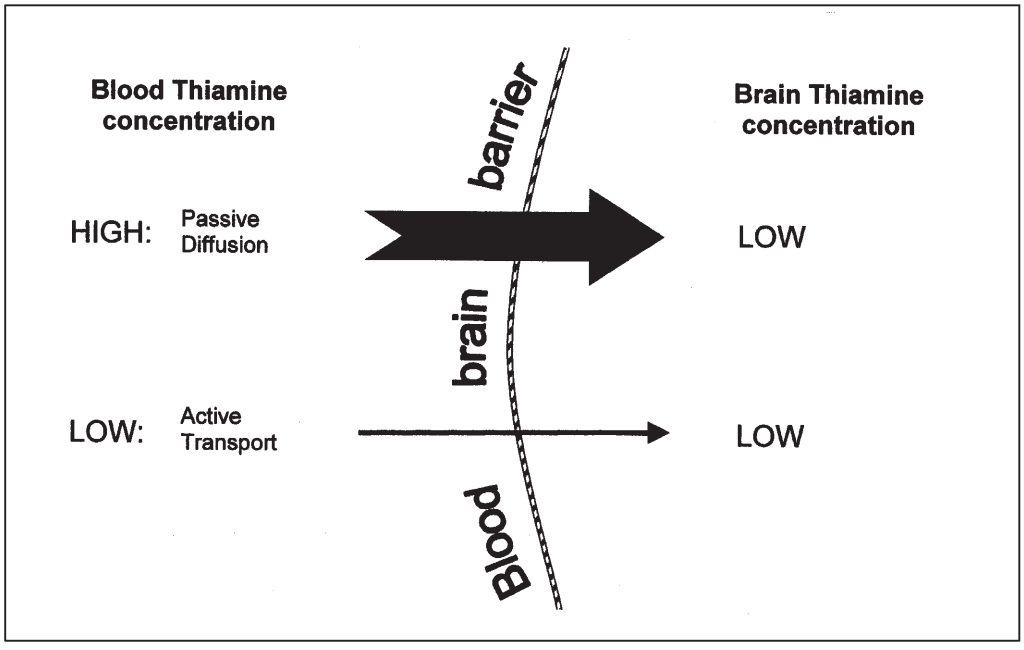

Fig. 3. Relative importance of passive diffusion and active transport in the rapid correction of depleted brain stores of thiamine after i.v. therapy. At normal physiological plasma concentrations of thiamine, influx into the brain is almost entirely due to a high-affinity carrier-mediated process (active transport) and occurs at a rate of 0.3 μg/h/g tissue (Greenwood *et al*., 1982) which is surprisingly similar to the rate of thiamine turnover in the brain (Rindi *et al*., 1980). High plasma thiamine levels provided by parenteral therapy permit rapid diffusion across the blood–brain barrier, providing therapeutic levels of brain thiamine. Thickness of the arrow indicates relative importance.

an intramuscular dose of ≥200 mg of thiamine may be required to show improvement in such a group. The importance of these findings must await further studies, however, since the improvement shown with the 200 mg dose was statistically marginal and there was a high rate of non-completion. It would also have been interesting to know whether a greater difference would have been seen in patients who were severely thiamine depleted.

In addition, significant magnesium deficiency occurs with chronic alcohol misuse (Flink, 1986). In the glycolytic pathway, converting glucose to pyruvate, there are seven key enzymes which require the divalent cation Mg^{2+} (Shils, 1996). Thiamine diphosphate (TDP) acts as a coenzyme to a number of intra-mitochondrial enzymes involved in carbohydrate metabolism, including the enzyme transketolase, which catalyses an important step in the pentose phosphate pathway. Mg^{2+} is also required as a co-factor for this enzyme and is thought to be involved in maintaining enzymic structure in a catalytically active form. Traviesa (1974) has demonstrated that patients with WE may be unresponsive to parenteral thiamine in the presence of hypomagnesaemia, but after correction of this deficit, the blood transketolase activity returns to normal, and there is clearing of the clinical signs. This may be the cause of occasional thiamine refractoriness in patients with acute WE (Traviesa, 1974). Further work is required to clarify the extent of this problem.

IS THERE A RISK OF ANAPHYLAXIS?

Many doctors will remember giving i.v./i.m. thiamine as 'Parentrovite', often by bolus injection, without the patient experiencing any adverse reactions. Wrenn and Slovis (1992) expressed the view that thiamine has an extremely high safety profile. They estimated that, 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. 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. Therefore >300 000 patients were treated without significant adverse reactions being reported. Wrenn and Slovis (1992) studied the clinical effects of i.v. thiamine in 989 patients and found 'minor reactions' (burning at injection site) in 11 patients and one case of generalized pruritus, indicating that thiamine administration is generally safe. However, anaphylactic responses do occur occasionally when B vitamins are given orally, i.v., i.m., or s.c., but are most often seen after multiple administrations when given i.v., on 'the end of a needle', as opposed to by an infusion over 30 min (Laws, 1941; Schiff, 1941; Stiles, 1941; Leitner, 1943; Reingold and Webb, 1946; Assem, 1973; Stein and Morgenstern, 1994).

In the UK, the British National Formulary (BNF) in March 1989 stated that 'The severe deficiency states WE and KP especially as seen in chronic alcoholism are best treated by the parenteral administration of B vitamins (Pabrinex and Parentrovite)'. These products contained equal amounts of thiamine together with a range of other vitamins. It is understandable that the Formulary should warn about the risk of anaphylaxis, and under the heading 'Thiamine' it states now (2001) that 'anaphylactic shock may occasionally follow injection'. The Committee on Safety of Medicines' (CSM) advice, since 1989 [The Joint Formulary Committee (1989)

British National Formulary *CSM Advice* September, No. 18, p. 322], has also included the following: 'Since potentially serious allergic adverse reactions may occur during, or shortly after administration, the CSM has recommended that: (1) use be restricted to patients in whom parenteral treatment is essential; (2) intravenous injections should be administered slowly (over 10 min); (3) facilities for treating anaphylaxis should be available when administered.'

However, Parentrovite was withdrawn in April 1989, and there is now only one formulation available (Pabrinex). Pabrinex is the only commercial multivitamin preparation currently available for parenteral use in the UK, and is available in a pack containing two vials. Vial no. 1 contains thiamine 250 mg, riboflavin 4 mg and pyridoxine 50 mg. Vial no. 2 contains nicotinamide 160 mg and vitamin C (ascorbic acid) 500 mg. The vials should be mixed immediately prior to use and are only presented in two separate containers to avoid long-term solubility problems.

It is possible that Pabrinex is associated with a lower incidence of adverse effects, yet the constraints of the earlier editions of the BNF remain, and the 2001 edition is substantially the same as that of 1989. The Royal College of Physicians advice recommends that Pabrinex be given by i.v. infusion over 30 min.

WHAT WAS THE BASIS OF CSM RECOMMENDATIONS?

The CSM reported serious allergic reactions following administration of parenteral B vitamins (Parentrovite). These included 90 reports of adverse reactions including 41 cases of anaphylaxis (two of these were fatal), 13 of dyspnoea/bronchospasm associated with i.v. administration and three anaphylactic reactions with i.m. between 1970 and 1988. During this 19-year period, one half to one million ampoules of each preparation of Parentrovite was sold annually in the UK, suggesting four reports of anaphylactic reaction reported for every one million pairs of i.v. ampoules or one report for every five million pairs of i.m. ampoules used. It was thought that the reaction was due to the thiamine present in the medication and it was recommended that administration should be by slow 10-min infusion. Although we have not seen the reports, it is understood that the majority of cases contained few details of the length of time of infusion. The CSM recommended stopping the infusion should a reaction occur. It becomes less clear how adequate treatment might be given under these circumstances. It has not been established what proportion of these reactions is anaphylactic (i.e. a true allergic reaction to thiamine) or anaphylactoid (i.e. a dose-dependent reaction) which might permit i.v. infusion over a longer time-interval should the patient be inadequately treated (e.g. half an hour).

The reaction has been attributed to non-specific histamine release (HR) (Lagunoff and Martin, 1983). Cases of anaphylactic shock have also been seen in patients with positive skin tests to vitamin B_1 (Pollit, 1968; Wrenn *et al*., 1989) and a case of reaction during desensitization has been reported (Mitrani, 1944). More recently, a patient was studied who had an IgE-specific anaphylactic response induced by thiamine (Fernandez *et al*., 1997). Leung *et al*. (1993) investigated two patients who had anaphylaxis to parenteral thiamine and demonstrated positive skin tests and positive oral challenge in one patient. This suggests that thiamine might have a direct action on mast cells or from IgE-mediated mast cell activation. It was of interest that thiamine contains a quaternary amine group to which IgE antibodies can bind (Leung *et al*., 1993). It should be stressed, as previously stated, that the risk is very low when compared with the incidence of a 1–10% chance of an allergic reaction to penicillin (0.04–0.27% chance of true anaphylaxis), a 2–3% chance of contrast media reaction and a 1–18% chance of an allergic response to streptokinase (Cook *et al*., 1998). In addition, the risk–benefit balance is overwhelmingly in favour of proceeding with thiamine treatment both on grounds of rarity of reactions and the fact that WE is a life-threatening condition. However, it is important to stress that the treatment should only be administered in circumstances where cardio-pulmonary resuscitation and i.v. (1:10 000) or i.m. (1:1000) (adrenaline) epinephrine are immediately available.

TREATING OUR PATIENTS

We have tried to define those patients who should be given a presumptive diagnosis of WE and those requiring prophylaxis (Tables 1 and 2). It is more difficult to give more precise advice about which specific patients require treatment with i.v. thiamine and about who should be responsible for the diagnosis and treatment. These have been discussed by Sowerby (1998). To be safe, the confused, ataxic drunk in A&E who has evidence of chronic alcohol misuse and has a poor diet, e.g. being of no fixed abode, should be given i.v. Pabrinex initially (by infusion over half an hour) whilst in A&E, irrespective of whether hospital admission is likely. It is hoped that, in future, many of these problems will be resolved as the need for treatment becomes more widely accepted.

Most patients undergoing detoxification in the community should be at little risk of WE, providing that patients at high risk have been excluded. However, there is an argument for assuming that all dependent patients are at risk given the high proportion of those with WE who are not detected until post-mortem examination (Harper *et al*., 1986).

The Royal College of Physicians' (2001) report has recommended that 'to prevent the neuropsychiatric complications of vitamin B deficiency in patients undergoing alcohol withdrawal in the community, high dose oral thiamine (200 mg per day) together with vitamin B strong tablets (30 mg per day), is the treatment of choice'. Assuming that oral thiamine absorption is adequate and that patients are compliant, mild depletion will be corrected. However, these recommendations will not provide adequate concentrations of thiamine in severely depleted patients. We do not know the incidence of brain lesions in patients treated in the community and the data are not available to enable us to define the groups of patients where thiamine malabsorption becomes a contributing and perhaps critical factor in the development of WE. However, it seems a reasonable assumption that the more malnourished the patient (especially in the presence of gross dietary deficiency, protein-calorie malnutrition, weight loss >20 lb in the preceding year, clinical signs of multiple vitamin deficiency, such as peripheral neuropathy, glossitis, scurvy etc.), the more they have been drinking and the more severe their clinical

state, including cirrhosis and other concurrent disease, the more likely they are to have impaired thiamine absorption. This does not take into account that some patients may be genetically predisposed to WE, but these cannot be identified at present. Recommendations for treatment of in-patients are given in Table 2.

WILL PATIENTS BE TREATED UNNECESSARILY?

Only ~12% of alcoholic patients show post-mortem evidence of WKS lesions in the diencephalic and brain stem regions (Torvik *et al*., 1982; Torvik, 1991). There is variability in the incidence figures of WE (Harper *et al*., 1995) which is probably due, at least in part, to differences in the criteria used for histological diagnosis and the frequency of alcohol misuse. However, the incidence is generally high (>1%) and generally >80% of those detected with the disease have a history of alcohol dependence (Torvik *et al*., 1982; Harper *et al*., 1986; Victor *et al*., 1989). Torvik (1991) reported that only a fraction of the cases discovered at autopsy (1–20%) are diagnosed clinically and that the wide spectrum of clinical symptoms has not been fully appreciated. We have no idea of the thiamine intake of these patients, nor of how many received thiamine therapy. However, it is possible that adequate nutrition or timely treatment might have prevented the brain damage that they sustained.

If all the alcoholic patients coming to post-mortem had been adequately treated, a significant proportion might not have died or might have avoided permanent brain damage. If it had been possible to identify reliably these WE patients ante-mortem, it would have been a matter of medical negligence if they had been left untreated. Given that reliable and specific identification of these patients ante-mortem is not in fact possible, the question therefore arises as to the number of patients who will be treated unnecessarily in order to ensure that such morbidity and mortality is prevented. The question of harm from anaphylaxis in this context is small, but deserves mention.

Reports of anaphylactic reaction with i.m. Pabrinex are only one report for every 5 million pairs sold. The argument for using i.v. therapy is to provide a high blood:brain concentration gradient as soon as possible in the initial treatment period. One feels that had there been an established way of confirming the diagnosis of WE on admission, as there is for myocardial infarction, then Pabrinex would have been given like streptokinase and nobody would have disagreed with this treatment. We consider, however, that the benefit to risk ratio is still in favour of treatment as indicated.

GENERAL CONCLUSIONS AND COMMENTS

Post-mortem findings indicate that we are failing to diagnose WE in up to 90% of patients, but there is no simple, reliable test available which will allow us to identify patients requiring urgent treatment. Therefore it is suggested that a presumptive diagnosis be made as indicated in Table 2.

Oral therapy is inadequate in patients who are considered to be at risk and thiamine must be given i.v. for prompt, effective correction of its depleted brain levels. In addition, the repeat A&E attender is unlikely to take oral medication regularly on discharge. Although anaphylaxis can occur, it is a rare event although facilities for resuscitation should always be available.

The Royal College of Physicians (2001) has supported a protocol for treatment within the A&E department (Table 1). Failure to enact this protocol risks litigation if the patient develops WE after leaving the A&E department. The continuation of care for patients admitted to hospital or treated in the community is very important and we have included a further protocol which it is hoped will be useful in the management of in-patients (Table 2). We hope also, in a future publication, to make recommendations for management of patients in the community.

More information is required on the extent of thiamine malabsorption in alcohol misuse, and it would be important to be able to identify patients who may be genetically predisposed to WE, so that prophylaxis may be considered. In the meantime, current knowledge dictates that our patients will be best served by our being always alert to the possibility of this diagnosis, especially in the frenetic environment of A&E, and by early treatment — perhaps whilst still drunk — by the most effective route under the circumstances which provides the greatest degree of safety for the patient.

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Editor's note — C. C. H. Cook and A. D. Thomson have received payment and expenses from Link Pharmaceuticals (manufacturers of Pabrinex) in respect of lectures and consultancy. Link Pharmaceuticals have also assisted them with the processes of literature searching and the undertaking of a survey on the use of Pabrinex.

R. Touquet has never received any fees at any time from Link Pharmaceuticals.

J. A. Henry does not have any conflict of interest in connection with this paper.

A. A.–B. B.