INVITED COMMENTARY

PARENTERAL THIAMINE AND WERNICKE'S ENCEPHALOPATHY: THE BALANCE OF RISKS AND PERCEPTION OF CONCERN

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Abstract — Wernicke's encephalopathy, a disorder with significant mortality and high morbidity, is common amongst alcohol-dependent patients. Thiamine deficiency appears to play a key role in its aetiology, and parenteral high-dose thiamine is effective in prophylaxis and treatment. Unfortunately, reports of rare anaphylactoid reactions have led to a dramatic reduction in the use of parenteral thiamine, and it is possible that this change in treatment has led, or will lead, to an increase in morbidity and mortality. There is a need for education of doctors who treat alcohol-dependent patients, in order to ensure appropriate use of parenteral thiamine in prophylaxis and treatment of this disorder.

INTRODUCTION

It is rare that a safe, available and effective treatment for a life-threatening disorder is not widely used in clinical practice. However, the perceptions of clinicians regarding the treatments that they use are influenced by a variety of factors. The medical education of undergraduates is supplemented by postgraduate training and then continuing medical education. Despite this, the priorities, risks and concerns that doctors perceive do not always accurately reflect the objective research evidence.

WERNICKE’S ENCEPHALOPATHY

Wernicke’s encephalopathy is a well-known complication of thiamine deficiency, which is known to be associated with alcohol misuse. The classical clinical features include ataxia, ophthalmoplegia and confusion, although none of these signs is invariable, and the presentation is often one of a non-specific confusional state. Mortality rates of 17–20% have been reported (Victor et al., 1989). In 85% of survivors, a chronic residual state, Korsakoff’s psychosis, is characterized by short-term memory loss but with relative preservation of other intellectual functions. Some 25% of patients developing Korsakoff’s psychosis require long-term institutionalization as a result of this, selective, organic brain damage (Victor et al., 1989).

The underlying histopathology is of microhaemorrhages in the mamillary bodies, dorso-medial nucleus of the thalamus, and peri-ventricular grey matter. These lesions appear to arise as a result of thiamine deficiency, although alcohol toxicity may also play a part (Lishman, 1990). Thiamine is a coenzyme involved in glucose and lipid metabolism and the production of amino acids and glucose-derived neurotransmitters (Greenwood et al., 1985; Thomson et al., 1987, 1994; Thomson, 1990; Thomson and Pratt, 1992). The three major thiamine-dependent enzyme systems are pyruvate dehydrogenase, transketolase and ketoacid decarboxylase (Thomson et al., 1987; Thomson and Pratt, 1992).

PROPHYLAXIS AND TREATMENT WITH PARENTERAL THIAMINE

For almost 30 years, until the late 1980s, the prevention and treatment of Wernicke’s encepha-
lopathy was managed by the parenteral administration of thiamine. Oral thiamine is very poorly absorbed in people who have been drinking heavily, or who are already malnourished (Thomson et al., 1970), and the high morbidity and mortality of this condition in any case suggest that vitamin levels should be restored as rapidly as possible. Intramuscular and intravenous injections were therefore the universally preferred routes of administration of thiamine supplements for patients who were at risk of, or actually suffering from, Wernicke's encephalopathy.

In 1989, the Committee on Safety of Medicines published a warning of serious adverse reactions relating to 'Parentrovite', which was at that time the only parenteral B vitamin supplement available for clinical use in the United Kingdom (Committee on Safety of Medicines, 1989). These adverse reactions are in fact extremely rare. The data represent approximately four reports of an anaphylactoid reaction for every million pairs of intravenous ampoules sold in the UK. For the intramuscular preparation, only 1 report has been made for 5 million ampoules sold. However, the concern raised by the Committee appears to have produced a disproportionate response, with many clinicians now prescribing oral thiamine for malnourished alcoholics at high risk of Wernicke's encephalopathy (O'Brien, 1995).

For some as yet unknown reason, possibly related to the reduction in use of parenteral B-complex vitamins, there was a 65% increase in hospital admissions for alcoholic psychoses in England over the period 1988–1994 (P. M. Hallwood, personal communication), despite the fact that both admissions for alcohol detoxification and alcohol consumption patterns have been constant over this time period (Thomas et al., 1994; Bennett et al., 1995). There is also more specific evidence that the incidence of Korsakoff's psychosis has been increasing over recent years, at least in one part of the UK (Ramayya and Jauhar, 1997).

While the risks of parenteral thiamine may have been overemphasized, it would seem that the risks of Wernicke's encephalopathy have been underestimated. Pathological evidence of Wernicke's encephalopathy is present at 1.5% of all post-mortems (Thomson and Pratt, 1992), and in 12.5% of alcoholics at post-mortem (Torvik et al., 1982). Mortality rates of 17–20% have been reported for Wernicke's encephalopathy, and 85% of the survivors go on to develop Korsakoff's psychosis. Furthermore, there is evidence that parenteral thiamine is effective in both prophylaxis (Williams and Long, 1968; Majumdar, 1980; Bligh and Madden, 1983) and in treatment (Cook and Thomson; 1997) of Wernicke's encephalopathy.

It would therefore appear that clinicians treating alcohol misusers have perceived a high risk of adverse reactions to parenteral thiamine, although the real risk is relatively small, and that this has resulted in reduced prescription of parenteral thiamine, even in cases where it is strongly indicated. On the other hand, it would appear that clinicians may have underestimated the risk of Wernicke's encephalopathy, which is both relatively common and associated with a high morbidity and mortality.

We would not wish to suggest that the warning published by the CSM was the only factor in precipitating the undesirable trend away from prescribing parenteral thiamine to patients at risk of Wernicke's encephalopathy. Withdrawal of 'Parentrovite' in November 1992, due to manufacturing problems, must also have played a part; a new product, 'Pabrinex', was introduced 9 months later. Lack of awareness of the prevalence and seriousness of Wernicke's encephalopathy must also have been a significant factor, and the condition is also difficult to diagnose reliably (Harper et al., 1986). However, all of these factors together have led to a misperception of the balance of risks and benefits to be achieved in the management of this condition and there has therefore been a major change in prescribing habits, which has been unintentionally detrimental to patients and contrary to the accumulated research findings.

If Wernicke's encephalopathy were easier to diagnose ante-mortem with specific, reliable, clinical signs and if the response to treatment was always dramatic, then we do not believe that the use of parenteral therapy would have been discontinued. It is because patients present with a diverse spectrum of signs and symptoms, some of which are due to irreversible brain damage and others due to confounding factors such as recent alcohol ingestion, that clinicians themselves have become confused and misled. It would also appear that the education of even the most experienced
CONCLUSIONS

It is vital that the facts concerning the prophylaxis and treatment of Wernicke's encephalopathy are brought to the attention of clinicians treating patients who misuse alcohol. Clear and objective guidance is needed in order that appropriate management of this condition becomes once more the norm, rather than the exception.

REFERENCES


