Letters to the Editor

Thiamine in Wernicke's syndrome – how much and how long?

Sir,
Wernicke's syndrome is well described as a manifestation of thiamine deficiency, particularly in alcoholics and hyperemesis gravidarum, yet the exact dose of thiamine, its method of administration and duration of treatment, both prophylactically and therapeutically, is unclear. This report illustrates the uncertainty that exists – an alcoholic was given oral thiamine prophylactically but still went on to develop Wernicke's syndrome. The discussion that follows looks at the available data on dose and duration of thiamine therapy in Wernicke's encephalopathy.

A 33-year-old woman was admitted with a haematemesis. She gave a four-year history of drinking one litre of vodka per day with an unsuccessful attempt at detoxification one year previously. Endoscopy revealed grade III oesophagitis with a hiatus hernia and omeprazole was commenced. Routinely she was started on oral thiamine 200 mg bid and Vitamin B complex one per day for the duration of her in-patient stay (12 days) and for one month thereafter. Her compliance was monitored in a residential detoxification unit.

Ten weeks later she represented with nausea and vomiting and was rehydrated intravenously with normal saline and 5% dextrose for three days. Towards the end of that time she suddenly developed diplopia. Ocular examination revealed skew deviation at rest, nystagmus in all directions with broken pursuit movements. Finger/nose and heel/shin testing was normal. However, on walking, the gait was unsteady and she was unable to perform tandem gait. Short-term memory was normal. Despite the previous thiamine supplement a clinical diagnosis of Wernicke's syndrome precipitated by dextrose infusion was made. She was treated with intravenous multibionta for six days (50 mg of thiamine per day) and oral thiamine 400 mg per day. Her symptoms gradually improved and after a two monthly follow-up she was left with a residual fine lateral nystagmus. Magnetic resonance imaging (MRI) of the brainstem carried out at the time of the crisis was normal.

The recommended intake of thiamine is 0.4 mg per 4200 kJ (1000 kcal) of diet, ie, 1–5 mg per day in adults with normal thiamine reserves. This represents protection from deficiency for a period of between 18 and 35 days. The maximum thiamine absorption following a single dose is estimated to be 5–15 mg though absorption may be increased by taking thiamine in divided doses with food. Subsequently alcoholics become thiamine deficient from a variety of causes including poor diet, decreased absorption, and metabolic derangement.

Sampling of literature reveals the *ad hoc* dosage regimes used to treat Wernicke's encephalopathy. Case reports which describe successful resolution of the condition (by definition presumably resulting in a positive reporting bias) have used a range of intravenous dosages between 100–500 mg per day.^{1–4} Other sources give unreferenced

Table Available preparations containing thiamine

Preparation	Company	Thiamine dose (mg)	Cost/dose (pence)*
<i>Intravenous</i>			
Multibionta	Merck	50	161
Pabrinex	Link Pharmaceuticals	250	174
Parentrovite	Bencard	250	discontinued
Thiamine (unlicensed)	Northwick Park Hosp	100	174
<i>Oral</i>			
Vitamin B compound	generic	1	0.35
Multivitamins BP	generic	1	0.75
Vitamin B compound strong	generic	5	0.50
Thiamine	generic	25	0.85
		50	1.45
		100	2.35
		300	3.70

*Drug tariff September 1994

figures of 50–300 mg per day.^{5–7} There are no data available on the duration of treatment, be it intravenous acute or long-term oral supplementation.

Current practice therefore relies on titration of the clinical state and biochemical parameters – an empirical option.

This report is instructive in outlining some of the difficulties that can occur in the treatment of putative deficiency states. Despite being provided with thiamine for 40 days, she still went on to develop brainstem signs when her thiamine requirement was increased by the inadvertent administration of glucose. Three learning points can be drawn from this (see box).

With these points in mind we would suggest that a reasonable (and unproven) strategy might be Pabrinex (intravenous high potency) two ampoule pairs over 10 minutes which may be repeated eight hourly for two days, followed by one ampoule pair intravenously per day until the patient can tolerate oral thiamine. This should be continued at 100 mg bid for at least three months and until the patient stops drinking. Available thiamine-containing preparations are given in the table.

Thiamine crises are common and neurologically devastating; however they are gratifyingly reversible and we believe a more concerted and logical approach is demanded.

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- 1 Ocakowski W, Kertesz A. Wernicke's encephalopathy after gastroscopy for morbid obesity. *Neurology* 1985; 35: 99.
- 2 Lonsdale D. Wernicke's encephalopathy: complication of intravenous hyperalimentation. *JAMA* 1978; 239: 1133.
- 3 Kwee I, Nakada T. Wernicke's encephalopathy induced by tolazamide. *N Engl J Med* 1983; 309: 599–600.

Learning points

- absorption of thiamine is impaired in alcoholics and a period of intravenous loading would seem to be essential
- if dextrose has to be used it should be preceded by intravenous thiamine, even if there is a recent history of thiamine administration
- thiamine supplementation should be continued as long as the patient remains an alcoholic

4 Raynar H, Craddock C. Reversible coma in Wernicke's encephalopathy. *Postgrad Med J* 1985; 61: 1097.

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6 Dollery C (ed). *Therapeutic drugs* 1st edn. London: Churchill Livingstone, 1991; T48–51.

7 Reynolds J (ed). *Martindale the extra pharmacopoeia*. London: Pharmaceutical Press, 1993; pp 1053–4.

Wernicke–Korsakoff syndrome due to hyperemesis gravidarum precipitated by thyrotoxicosis

Sir,
Wernicke's classical triad (see box) is only part of the wide variety of presenting features that make up the eponymous encephalopathy.¹ We report a 30-year-old lady who presented 19 weeks into pregnancy with prolonged vomiting and 8 kg weight loss in the previous two months. Five days before admission she refused further food and became increasingly lethargic, finally taking to her bed. Her first pregnancy had been ectopic, and she was otherwise well. She denied smoking, alcohol ingestion, and was only taking anti-emetic medication.

On examination she was obtunded, her skin turgor was reduced and mild jaundice was

present with a metabolic 'flap'. There were no stigmata of chronic liver disease. Pupil reaction was noted as 'sluggish', and nystagmus was present, more marked in the horizontal plane, the remainder of the cranial nerves were normal. The ankle reflexes were absent, but the physical examination was otherwise normal. Investigations, including a clotting screen, were normal except urea 19.3 mmol/l (normal 3–7 mmol/l), bilirubin 75 mmol/l (normal 3–17 mmol/l), haemoglobin 9.3 g/dl. Ultrasound confirmed live twin pregnancy and the mother's liver and renal tract were normal.

She received intravenous rehydration and high dose vitamin supplementation including thiamine. Anti-emetic drugs failed to stop the vomiting. Thyroid function tests subsequently returned with a TSH 0.08 mU/l (normal 0.32–5.0) and free thyroxine 38.7 pmol/l (normal 9–24). She received propranolol for three days and propylthiouracil. After a further week the vomiting desisted.

During recovery she was vague, forgetful and ignored personal hygiene. Her relatives confirmed a change from her pre-morbid state. A mental state examination revealed loss of short-term memory, confabulation, and poor orientation in time only. Truncal ataxia was noted, but her neurology was otherwise normal. A computed tomography (CT) scan of the brain showed only mild ventricular dilatation. The haematology, biochemistry (except thyroid function), microbiology and virology screen, electroencephalogram, and cerebrospinal fluid were normal or negative.

Vitamin supplementation continued and the nystagmus disappeared by day 5 and the vomiting by day 7. The twins were born at 29 weeks gestation with severe hyaline membrane disease but three years later both are well. After childbirth, the mother's thyroid function normalised and treatment stopped. Her CT scan was normal 8 months later and her only residual symptom is impaired short-term memory.

Wernicke's encephalopathy complicating hyperemesis gravidarum was first reported in 1914 and since then approximately 14 cases have appeared in the literature.^{2–4} The mean age of the patients was 26 years (range 18 to 35 years) and their symptoms occurred between the 14th and 20th week of pregnancy (median 15 weeks) after at least three weeks of persistent vomiting. Only half of these pregnancies resulted in normal healthy children, and symptoms persisted in three although the follow-up interval was variable. A single report describes a 61-year-old lady with thyrotoxicosis who developed Wernicke's encephalopathy after excessive vomiting.⁵ We believe our patient is the first to be described with hyperemesis gravidarum aggravated by twin pregnancy and thyrotoxicosis that subsequently developed Wernicke's encephalopathy.

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Wernicke's encephalopathy: classical features

- confusion
- nystagmus
- ataxia

- 1 Wernicke C. In: *Lehrbuch der Gehirnkrankheiten für Ärzte und Studieren*. Kassel: Theodore Fischer, 1881, vol 2, p 229.
- 2 Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. *N Engl J Med* 1985; 312: 1035–9.
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- 4 Galloway PJ. Wernicke's encephalopathy and hyperemesis gravidarum [letter, comment]. *BMJ* 1992; 305: 1096.
- 5 Enoch BA, Williams DM. An association between Wernicke's encephalopathy and thyrotoxicosis. *Postgrad Med J* 1968; 44: 923–30.

Peritonitis complicating leptospirosis

Sir

Leptospirosis is an acute generalised infectious disease, characterised by extensive vasculitis. All organ systems may be involved. The rare complications include acute cholecystitis, myocarditis, pancreatitis, parotitis, and epididymo-orchitis. To the best of our knowledge, peritonitis complicating the course of leptospirosis has not been reported so far. Serum aminotransferase elevation in leptospirosis is rarely more than five-fold, regardless of the degree of hyperbilirubinemia – bilirubin levels may be as high as 1111.5 µmol/l.¹ We report here a patient with leptospirosis and peritonitis with marked elevation of aminotransferases.

A 32-year-old male scientist working with laboratory animals presented with a 10-day history of high fever associated with myalgias. He developed progressive deterioration in sensorium three days prior to admission. On presentation the patient was febrile, comatose, and jaundiced. The conjunctivae were suffused. Examination of the heart and chest was unremarkable. Meningeal signs were absent and no focal neurological deficit was noticed. The patient had splenomegaly of 2 cm. There was no clinical evidence of free fluid in the abdomen. Investigations on admission revealed a haemoglobin of 91 g/l, total leucocyte count of $12.2 \times 10^9/l$ (polymorphonuclear neutrophils 63%, lymphocytes 37%) and a platelet count of $123 \times 10^9/l$. Blood sugar and electrolytes were within normal limits. Blood urea nitrogen was 13.57 mmol/l and serum creatinine 344 µmol/l. Urinalysis showed proteinuria of 2+ (24-h excretion 0.8 g) and 1–2 red blood cells per high-powered field. Liver function tests revealed a serum bilirubin of 53.01 µmol/l and serum alkaline phosphatase of 236 IU/l. Aspartate transaminase and alanine transaminase were 4918 IU/l and 2309 IU/l, respectively, almost a 100-fold elevation. Total serum proteins, albumin, and globulin were 47, 23, and 24 g/l, respectively. Prothrombin time was 21 s (control 12 s). Serum creatine phosphokinase was 440 IU/l. CSF examination was unremarkable. Arterial blood

gas analysis showed mild metabolic acidosis. Chest X-ray and electrocardiogram were normal. Blood and urine cultures were sterile. A provisional diagnosis of leptospirosis was made and the patient was started on intravenous penicillin G (1.5 million units six hourly) along with supportive treatment. On admission leptospiral serology done by indirect haemagglutination and microscopic agglutination using pooled antigen was negative. Leptospiral serology repeated 10 days after admission showed a four-fold rise in titres. Serotype determination could not be done.

On the third day of hospitalisation the patient developed progressive distension of abdomen with rigidity and rebound tenderness. Plain X-rays of the abdomen did not show any air under the diaphragm. Ultrasound and contrast-enhanced CT scan of the abdomen showed ascites and splenomegaly. A litre of straw-coloured ascitic fluid was tapped. It had a protein content of 26 g/l with a white blood cell count of $0.5 \times 10^9/l$, mainly polymorphonuclear leucocytes. Cultures of ascitic fluid were sterile. During his hospital stay the patient's renal parameters deteriorated and he was given hemodialysis three times. After a week the patient's clinical condition gradually improved with reduction in ascites and progressive improvement in biochemical parameters. The renal and liver function tests returned to normal at the end of seven weeks.

Leptospirosis presents in various ways, from inapparent to fulminating and fatal infection. Confirmation of diagnosis is either by isolating the organism or more commonly, by detecting antibodies in the patient's blood.² Peritonitis in leptospirosis may be explained on the basis of immuno-inflammation due to leptospiral antigens during the immune phase. Since culture of the ascitic fluid was sterile a superimposed infection seems unlikely in our patient. Liver involvement in leptospirosis is usually associated with mild elevation of aminotransferases.³ Our patient exhibited more than 100-fold elevation in aspartate transaminase and alanine transferase. This is an unusual feature. However, as expected, the abnormalities in the liver function tests returned to normal with no evidence of residual hepatic damage.

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