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Lesson of the month (2)

The ataxic cirrhotic

Hepatic cirrhosis secondary to excess alcohol consumption is increasing in incidence, and these patients can develop ataxia secondary to direct toxic effects of alcohol on the cerebellum. However, it is important to remain vigilant for other causes of an unsteady gait, including space-occupying lesions and medications, such as phenytoin. Patients with hypoalbuminaemia, such as those with cirrhosis, are more prone to developing toxic effects from phenytoin, as this Lesson describes. Therefore, dose adjustments might be necessary.

Lesson

A 50-year-old unemployed woman presented in September 2011 to the emergency department having sustained a minor head injury following a fall. Non-contrast cranial computed tomography was normal and so she was admitted under the general medical team for assessment of falls and for further rehabilitation. She had a past history of a traumatic subarachnoid haemorrhage managed conservatively but complicated by seizures, right-sided breast cancer, for which she had undergone a mastectomy and lymph node clearance, hepatic cirrhosis secondary to chronic alcohol abuse (currently drinking 80 units per week), pancytopenia secondary to alcohol, and dyslipidaemia. She was taking ramipril 2.5 mg daily, phenytoin 300 mg daily, thiamine 100 mg twice daily, vitamin B compound strong 1 tablet twice daily and folic acid 5 mg daily. She lived with her husband, also an alcoholic, and she was considered to be a vulnerable adult.

On examination, she appeared unkempt with widespread bruising, but was normothermic (37.0°C); her pulse was 72 beats per minute and regular, and her blood pressure was 128/82 mmHg with no postural decrease. General examination revealed numerous spider naevi, an early right-hand Dupuytren's contracture and decreased muscle bulk consistent with hepatic cirrhosis together with asterixis. There were no audible cardiac murmurs. Respiratory and abdominal examinations were both unremarkable. On neurological examination, she had florid bidirectional horizontal nystagmus, bilateral intention tremor, past pointing and mild dysarthria, with no other speech disturbance. She was profoundly ataxic but maintained truncal stability; she commented that her balance had been poor for some time. Her Glasgow coma score was 15, with an abbreviated mini mental test score of 6/10.

Initial laboratory investigations revealed her full blood count to be: haemoglobin 12.4 g/dl (MCV 108.2 fl), white cell count 2.09×10^9/l and platelets 49×10^9/l. Her international normalised ratio (INR) was elevated at 1.5. Renal function was normal, although she was mildly hypokalaemic at 3.3 mmol/l, with a normal magnesium, calcium, phosphate and sodium. Liver function tests were abnormal with albumin 28 g/l, bilirubin 39 µmol/l, alkaline phosphatase 203 IU/l and alanine transaminase (ALT) 52 IU/l. An electrocardiogram showed sinus rhythm with no conduction delay. A chest X-ray showed no abnormalities.

An initial diagnosis of alcohol-induced cerebellar damage with hepatic encephalopathy was made by the admitting medical team. Management comprised high-dose combined B vitamins (Pabrinex®) to correct any element of Wernicke–Korsakoff's syndrome, chlordiazepoxide for alcohol withdrawal, lactulose to prevent constipation-induced encephalopathy, and involvement of physiotherapy and occupational therapy for rehabilitation. Magnetic resonance imaging of the posterior fossa was scheduled to exclude cerebellar metastases from her breast cancer, but before this could be performed, a further laboratory result was received.

She had marked phenytoin toxicity with a level of 30.9 mg/l (therapeutic level 10–20 mg/l). On further examination, she had marked gingival hypertrophy and hirsutism (Fig 1). Her phenytoin was stopped and, after discussion with the neurology consultant, was reintroduced at a lower dose, 225 mg daily, once the level was <18 mg/l. At the point of discharge, 14 days later, her cerebellar symptoms had improved significantly and she was able to walk with a zimmer frame and transfer unaided. She had a therapeutic phenytoin level.

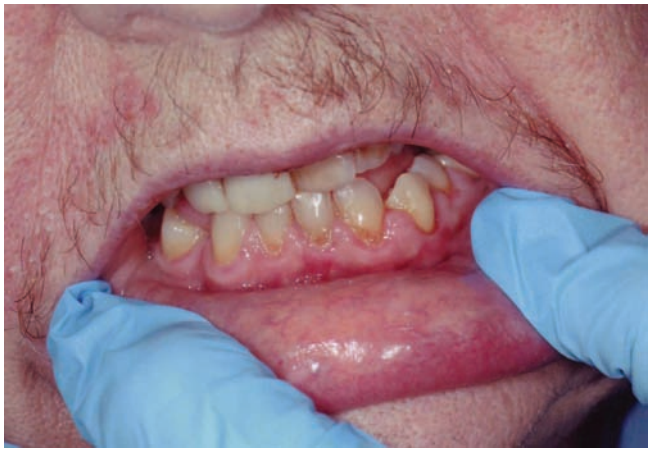

Fig 1. Photograph demonstrating gingival hypertrophy and hirsutism.

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Discussion

Phenytoin is used in the treatment of all forms of epilepsy, with the exception of absence seizures, and is indicated as therapy for benzodiazepine-resistant status epilepticus. Its mode of action is not entirely clear but involves the blockade of voltage-gated sodium channels in neurons. It is related, in chemical structure, to barbiturates and is metabolised through hydroxylation by the cytochrome P450 enzymes CYP2C9 and CYP2C19. Genetic polymorphisms of these enzymes might also affect its pharmacology.[1] The rate of phenytoin metabolism is dose dependent, with lower doses being metabolised via first-order kinetics and higher doses by zero-order kinetics.[2] Within plasma, it is extensively (>90%) bound to plasma proteins, particularly albumin, and it is only the unbound fraction that exerts biological activity and results in seizure control. Thus, individuals with hypoalbuminaemia (including nephrotic syndrome, hepatic cirrhosis and severe malnutrition) have a greater proportion of unbound phenytoin and a greater propensity to develop phenytoin toxicity if levels are not monitored. It undergoes renal excretion.

Hepatic cirrhosis is increasing in incidence,[3] with a large number of cases caused by excessive alcohol consumption. Biochemically, it can be characterised by a decreased serum albumin and often abnormalities of other liver function tests, such as bilirubin, ALT and gamma-glutamyl transferase (GGT). Other laboratory markers of cirrhosis include an elevated INR, thrombocytopenia and macrocytosis (often in the presence of a mild anaemia). Not only is the hypoalbuminaemic state important with regard to phenytoin levels, but it is also well recognised that chronic alcohol consumption activates cytochrome P450 enzymes, resulting in an enhanced breakdown of drugs metabolised by this system. Other drugs that interact with this enzyme system will also affect phenytoin levels. Despite this, phenytoin remains a good choice for control of epilepsy in patients with alcoholism because of its broad therapeutic spectrum and relative ease of administration, with a once-daily dose and no need for titration.

Phenytoin blood levels should be obtained immediately predose (trough), but it is important to recognise that the result does not differentiate between bound and unbound drug. In a patient with hypoalbuminaemia, the fraction of bound drug might decrease, resulting in an increase in the free fraction. Therefore, even at therapeutic levels (typically 10–20 mg/l), these patients can develop toxicity. The Sheiner–Tozer equation can be used to adjust for both low albumin and abnormal renal function:[4]

$$\text{Corrected phenytoin (mg/l)} = \frac{\text{measured Phenytoin (mg/l)}}{(\text{adjustment} \times \text{albumin (g/dl)}) + 0.1}$$

Adjustment = 0.2 (or 0.1 if creatinine clearance <20)

For our patient, her corrected phenytoin level at admission was calculated to be as follows: $30.9/((0.2 \times 2.8)+0.1)=46.8$ mg/l (note that albumin is measured in g/dl not g/l).

Symptoms associated with phenytoin toxicity increase in severity with increasing plasma levels. It is unusual to get adverse symptoms with a level <20 mg/l, but as levels increase, patients can develop nystagmus, ataxia, slurred speech, confusion and, ultimately, coma and even death. In the acute overdose setting most, if not all, of these symptoms are reversible, but this might not be the case in patients with chronic overexposure.

The liver is a site for metabolism of a range of drugs and this case highlights the need to consider adverse effects from prescribed medications as a cause for acute medical admissions. Patients with hepatic cirrhosis might need dose adjustments made, particularly of medications that are affected by serum albumin levels and alcohol ingestion. With the increasing levels of cirrhosis, this might become a more prevalent problem and one which we feel that all physicians should be aware of.

References

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