CASE REPORT

When less is more: a case of phenytoin toxicity

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SUMMARY

The authors present a case of an 87-year-old gentleman who presented with general deterioration, increased confusion, recurrent falls and unsteadiness. He was treated for a urinary tract infection but was found to deteriorate rapidly, developing bilateral nystagmus, marked pastpointing, dysarthria and central ataxia. He had a complex medical history including epilepsy controlled with long-term phenytoin. Phenytoin is 90% protein bound and displaced by bilirubin. At the time of deterioration his total phenytoin concentration was within the limits of the laboratory's recommended therapeutic range. The biochemistry report also denoted the patient was hypoalbuminaemic and hyperbilirubinaemic. His symptoms completely resolved with phenytoin dose reduction. The combination of low albumin and high bilirubin may cause an increase in the free phenytoin concentration, resulting in toxicity, despite the measured total phenytoin concentration being within the therapeutic interval.

BACKGROUND

- ▶ Phenytoin is a common drug with well-recognised side effects.
- ▶ Importance of high index of suspicion for subacute toxicity.
- ▶ Awareness of protein–drug binding pharmacokinetics.
- ▶ Knowledge that reported drug concentrations must be interpreted in their clinical context.

CASE PRESENTATION

An 87-year-old man, was referred by his general practitioner to hospital with a 1-week history of feeling unwell and 'off legs', with episodic confusion and reduced mobility due to feeling weak and unsteady. His wife reported that he had been in a state of general decline over the previous 6 months with frequent falls, and that he seemed increasingly muddled and unable to read the newspaper. Owing to his frequent falls, he had opted to have a long-term urinary catheter, rather than risk falling when walking to the toilet at night.

Upon examination, he was alert and orientated. He was not jaundiced and there was normal power, sensation, reflexes and coordination of both upper and lower limbs. He was noted to have mild diplopia and nystagmus at the extremes of gaze. His blood tests upon admission showed an elevated C reactive protein of 63, baseline bilirubin of 17 and albumin of 32 but were otherwise within reference intervals.

The patient had a complex medical history, having been diagnosed with high-grade superficial transitional cell carcinoma of the bladder in 2009,

for which he had received intravesical BCG therapy. Unfortunately, he subsequently developed invasive tuberculosis (TB) cystitis and was started on quadruple antiTB therapy, comprising rifampicin, isoniazid, ethambutol, and pyrazinamide, 6 months previously. He was also on long-term phenytoin for epilepsy, following a seizure after a small stroke 30 years previously. He had been seizure-free for more than 10 years but had continued phenytoin to allow him to continue driving.

At the time of admission, the cause of his general decline was unclear. He had been admitted 2 months previously with similar symptoms but had improved during the admission and was discharged without a clear unifying diagnosis. A CT head showed periventricular white matter low attenuation consistent with small vessel ischaemia but no acute infarct, intracranial bleed or lesion was seen. A catheter urine specimen showed a profuse growth of *Escherichia coli* and his symptoms were initially attributed to a urinary tract infection (UTI), which was treated with amoxicillin. Despite antibiotic treatment, he continued to deteriorate over the next 7 days, becoming more confused and complaining of dizziness, nausea and vomiting. He was noted to be intermittently dysarthric and began to have difficulty swallowing food and drink, choking due to both. He was kept nil by mouth due to the risk of aspiration but repeatedly declined nasogastric feeding. Owing to his poor oral intake, his albumin dropped rapidly to 24 g/l.

Ten days after admission, he became noticeably icteric and had bilateral nystagmus at rest with new onset cerebellar signs of past pointing, intention tremor and central ataxia. A repeat CT head showed no change from the previous scan but his bilirubin was noted to have increased sharply since admission from a baseline of 17–92 µmol/l, while alkaline phosphatase and alanine transaminase were within reference ranges. Owing to his symptoms, the suspicion of phenytoin toxicity was raised but his reported phenytoin concentration was at the upper limit of the recommended therapeutic interval at 79 µmol/l (range 40–80 micromol/l). Nevertheless, with multiple confounding comorbidities, polypharmacy and the absence of a clear diagnosis, his phenytoin dose was decreased by half from 200 to 100 mg once daily. His symptoms markedly improved with the reduction in phenytoin dosage. The cerebellar signs, dysarthria, poor swallow and confusion resolved completely and he and his wife were pleased to report that he was 'back to (his) old self'.

DIFFERENTIAL DIAGNOSIS

The authors suggest that the patient had been suffering from chronic phenytoin toxicity secondary

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to low albumin since the introduction of his antiTB medication and subsequent loss of appetite. His isolated bilirubin rise is attributed to Gilbert's syndrome, likely secondary to the concurrent UTI, reduced oral intake and the stress of hospital admission. In the absence of other abnormal liver function tests, it was felt unlikely to be caused by drug-induced hepatotoxicity. The combination of low albumin and elevated bilirubin contributed to a sudden increase in the free phenytoin levels, resulting in overt symptomatic toxicity causing new onset cerebellar signs which resolved completely upon reduction of the phenytoin dose.

OUTCOME AND FOLLOW-UP

Upon review of his biochemistry, the patient's albumin was noted to have been steadily decreasing since the introduction of the antiTB medications and the patient reported that he had lost his normally prodigious appetite since starting them. The patient's symptoms of nystagmus, ataxia and confusion resolved completely after the reduction of his phenytoin dose. He was reviewed by the Infectious Diseases team and, after discussion with the patient and his wife, his antiTB medications were stopped, having completed a 6 month course of treatment. His appetite subsequently improved, with a corresponding rise in his albumin levels and he was discharged home with a package of care. Follow-up was arranged with the Infectious Diseases clinic. Measurements of phenytoin concentration: both free and bound, has been discussed with the Consultant Chemical Pathologist in the Department of Clinical Biochemistry.

DISCUSSION

Phenytoin is a commonly used antiepileptic drug. It is used as an adjunct in seizure prevention in poststroke patients and is the first-line antiepileptic in neurocritical care of brain injury patients. Phenytoin is 90% bound to albumin but only unbound 'free' phenytoin crosses the blood brain barrier and can exert control over neuronal firing and cause toxicity symptoms. A recent update of the National Institute for Clinical Excellence guidance on the treatment of epilepsy warns of the dangers of polypharmacy and comorbidity affecting the pharmacokinetics of antiepileptic medications in older patients.¹

Case literature describes phenytoin toxicity in patients with poor nutrition. Critically ill patients with low albumin levels and concurrent phenytoin therapy can exhibit signs of phenytoin toxicity despite measured phenytoin concentration being within the therapeutic interval.² Hypoalbuminaemia has been shown to be positively correlated with concentrations of free phenytoin. In these patients, calculated free phenytoin using the Sheiner-Tozer equation underestimates free concentration with a potential to misguide therapy.³ In addition, several circulating substances such as free fatty acids and bilirubin competitively bind albumin and can displace phenytoin from its bound state.⁴ A sharp rise in bilirubin saturates the binding sites on serum protein, thus reducing the availability for phenytoin and potentiating free phenytoin concentration. This effect has been demonstrated with other protein-bound drugs in patients with a similarly deranged biochemical picture.^{5 6}

It is thought that this patient's free phenytoin concentration is likely to have been significantly higher in the context of his low albumin and raised bilirubin. Laboratories do not routinely measure free phenytoin as the techniques of dialysis or ultrafiltration are not warranted in the majority of patients.⁷ In this particular case, direct laboratory measurement of free phenytoin level would have helped guide management. Knowledge of the combined effect of low albumin and high bilirubin influencing free phenytoin levels might have contributed to an earlier definitive diagnosis in the patient.

Learning points

- ▶ Phenytoin is a common drug with numerous side effects.
- ▶ Phenytoin is 90% protein bound; reported values are routinely only protein-bound concentrations.
- ▶ It is important to consider symptomatic phenytoin toxicity in the context of hypoalbuminaemia and hyperbilirubinaemia even with apparently 'normal' phenytoin concentration.
- ▶ This case supports the need for free phenytoin concentration monitoring in specific cases where there is clinical suspicion.

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Contributors The case was managed by IA ward consultant, who initially suggested the diagnosis and KR and CBvS were junior ward doctors caring for the patient. KR had the idea to submit this as a learning case report and wrote the case history. CBvS critically reviewed the manuscript for intellectual content, wrote the discussion and edited the manuscript. IA contributed by critically reviewing and editing the manuscript. All authors approved the final draft of the manuscript. This case has not been submitted anywhere else and is an original work.

Competing interests None.

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