CASE REPORT

Phenytoin-induced hypothermia

Marianne Watters, Hilary Wilson, Pamela Everitt

Department of Rheumatology,
Glasgow Royal Infirmary,
Glasgow, UK

Correspondence to
Dr Marianne Watters,
marianne.watters@nhs.net

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SUMMARY

A 60-year-old man with cerebral palsy and epilepsy was admitted with acute lethargy and deterioration in coordination. He was noted to be hypothermic at 35°C on admission. Routine work-up revealed toxic levels of phenytoin. No cause of hypothermia could be identified but as his phenytoin levels normalised, his body temperature also improved. There are three other reported cases of phenytoin-induced hypothermia in the literature. Could this be a rare cause of hypothermia?

BACKGROUND

This case highlights the importance of considering unusual causes of hypothermia and the potential side effects of commonly used drugs such as phenytoin.

Case presentation

A 60-year-old man with cerebral palsy was admitted via acute medical receiving with a 3-day history of noticeable change in behaviour. His brother (primary carer) reported that he had become more withdrawn and lethargic. His co-ordination had deteriorated: he was noted to be dropping cups when drinking and not putting food in his mouth properly. His brother also reported that he felt cold.

On admission, he was found to be hypothermic with a temperature of 35°C. This persisted after BearHugger heating was applied and continued to fluctuate between 33.2°C and 36.3°C over the following days. All other observations were normal. He had a grossly normal examination with the only positive finding of horizontal nystagmus. His medical history included cerebral palsy, tuberculosis (1958), meningitis (1958), epilepsy (1966), deep vein thrombosis (DVT) (2013), transient ischaemic attack (TIA) (2013).

A routine nursing assessment of swallow was carried out, and his swallow was deemed unsafe. In view of this, his routine oral medications were withheld and those deemed to be essential (phenobarbital and phenytoin for seizure control) were converted from normal oral dose to intravenous. Twenty hours after admission, the patient had a self-terminating tonic-clonic seizure lasting approximately 1 minute. This prompted the investigation of phenytoin blood level, which was found to be dangerously high.

Investigations

Admission investigations were aimed at identifying a possible underlying cause of hypothermia

and change in behaviour. These included normal chest X-ray and normal CT head. An ECG showed prolonged QT interval. Urea and electrolytes, full blood count, C-reactive protein (CRP), calcium and liver function tests were normal. Capillary blood glucose was 6.1. Blood phenytoin level was found to be 38.5 mg/L (10–20 mg/L), and phenobarbital was 26.4 mg/L (15–40 mg/L).

Differential diagnosis

The main differential diagnosis was sepsis. This was ruled out after white cell count (WCC) and CRP were found to be normal, and no focal infection could be identified.

Treatment

Phenytoin was withheld, and plasma blood level was monitored over the following days. A Bear-Hugger heating system was also applied aiming to elevate body temperature with external heat.

Outcome and follow-up

The phenytoin level gradually reduced to fall within normal range over 3–4 days. During this time period, temperature recordings also showed a trend towards improvement and eventually normalised. The patient has been on the same regimen of anti-epileptic medication for many years but following this episode referral was made to neurology for consideration of treatment adjustment given the toxic phenytoin levels recorded.

DISCUSSION

Phenytoin is a first generation anticonvulsant used to treat status epilepticus, tonic-clonic and partial seizures.¹ The mechanism of action is not fully understood but it is thought to stabilise seizure threshold and prevent dissemination of seizure activity through non-synaptic, presynaptic and postsynaptic actions in the motor cortex.² Oral maintenance dosing ranges from 3 to 5 mg/kg daily for adults, and the desirable therapeutic range is 10–20 mg/L.^{2,3} It is highly protein bound and is extensively metabolised through the cytochrome P450 system. Phenytoin has an unusual pharmacokinetic profile where it follows non-linear kinetics due to enzyme saturation. This means there is constant phenytoin metabolism and a small increase in dose can result in disproportionately high serum levels and toxicity.² Due to the narrow therapeutic window of phenytoin, drug interactions can be clinically significant and clinicians must prescribe with caution.³ Phenytoin is metabolised by isoenzymes

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CYP2C9 and CYP2C19. Therefore, any drugs which inhibit or induce these enzymes may affect phenytoin metabolism.⁴ It is also an isoenzyme inducer so can interfere with the metabolism of other drugs.²

Phenytoin toxicity can manifest as central nervous system dysfunction. The most common symptoms being nausea, confusion, ataxia and nystagmus.⁵ In our case, the history given by the patient's brother documented instances of lack of coordination such as dropping cups and nystagmus were noted on initial routine examination.

There are three other case reports in the literature which report phenytoin toxicity as the cause of hypothermia.^{6–8} In one case, the underlying cause of hypothermia was found to be related to hypoadrenalism.⁸ The authors argue that this may have been precipitated by phenytoin toxicity. They suggest that phenytoin may produce hypothermia indirectly via induction of hepatic cytochrome P450 enzymes and stimulation of steroid clearance, which could lead to the induction or exacerbation of adrenal insufficiency in certain patients. In the other cases^{6,7} no underlying cause such as hypoadrenalism was reported. In all cases, hypothermia induced by phenytoin toxicity was supported by finding that as phenytoin levels decreased back to normal range normalisation of temperature also occurred. This was demonstrated in our case report.

During the initial work-up of the patient in our case, sepsis was considered the main differential diagnosis. This was made unlikely by a normal CRP and WCC. Further investigations were carried out including pituitary function, short synacthen and thyroid function tests. These were found to be normal.

It has been suggested that hypothermia may be mediated by the effect of phenytoin on the hypothalamus. There are a number of studies using an animal model which have demonstrated the ability of phenytoin to lower body temperature.⁹

It is unclear why the patient in this case report developed toxic levels of plasma phenytoin when it was claimed that he had been taking the same prescribed dose without harm for many years. It is possible that the patient had accidentally taken excessive doses or there was a misunderstanding of the prescription order. These are the most common reported causes of acute phenytoin intoxication in a case-series study of 30 patients.¹⁰ Furthermore, phenytoin levels were retrospectively added to blood samples taken on admission, which confirmed high levels of serum phenytoin prior to the intravenous dose given shortly after admission. There is a possibility that the toxic levels of phenytoin were in fact caused by hypothermia. This has been documented in the literature. For example, in a study of the effect of therapeutic hypothermia on phenytoin pharmacokinetics, significantly higher plasma concentrations and reduced elimination during hypothermia were found.¹¹ Investigations carried out during admission could not identify any pathological cause of hypothermia such as hypopituitary dysfunction. It is a

possibility that environmental conditions prehospital admission may have caused the patient to experience hypothermia, but there is no evidence of neglect or concern in the social background of the case.

It is difficult to prove a definitive causative relationship between phenytoin and hypothermia but in this case and the three others reported, normalisation of phenytoin levels led to normalisation of temperature.

Learning points

- Phenytoin toxicity can present with ataxia and nystagmus. These findings are common in patients at risk of Wernicke's encephalopathy but consider other causes such as drug toxicity.
- Consider measuring blood levels of antiepileptic drugs in patients who present with change in behaviour.
- Potential medication side effects should be fully explored whenever there is difficulty in establishing diagnosis.

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