CASE REPORT

Successful use of haemodialysis to treat phenobarbital overdose

Kimberley Hoyland,¹ Michael Hoy,¹ Richard Austin,¹ Martyn Wildman²¹Department of Intensive Care, Lister Hospital, Stevenage, Hertfordshire, UK²Department of Intensive Care and Anaesthetics, Lister Hospital, Stevenage, Hertfordshire, UK

Correspondence to

Dr Kimberley Hoyland, kimberley.hoyland@nhs.net

SUMMARY

A 50-year-old woman presented with coma caused by a phenobarbital overdose, requiring intubation and admission to critical care. She was an international visitor and had been prescribed the drug for night-sedation. Phenobarbital is a long-acting barbiturate, which in an overdose can cause central nervous system depression, respiratory failure and haemodynamic instability; these patients can remain obtunded for many days. After initial supportive therapy, she was dialysed to help in the elimination of the drug. Haemodialysis resulted in a markedly reduced plasma level of phenobarbital, which decreased the length of intubation and stay in the critical care unit and aided full recovery.

BACKGROUND

Barbiturates bind to the β -subunit of the γ -aminobutyric acid A (GABA-A) receptor, increasing the duration of the opening of the chloride ion channel and potentiating the neuroinhibitory effect of GABA. The channel kinetics of the GABA-A receptor have been explained by a three-state model with chloride channel open-time constants of 1, 4 and 11 ms—opening more frequently and moving from a lower to a greater state as GABA concentration increases.¹ Barbiturates promote the opening of GABA-A receptors in their longer lived state and at a higher frequency. It has been shown that in higher doses, barbiturates directly stimulate GABA-A receptors outside of the presence of GABA itself.² The net effect of barbiturates is one of neuroinhibition, and as such they have evolved multiple clinical applications, including as anxiolytic, sedative, antiepileptic and anaesthetic agents.

Phenobarbital is a long-acting barbiturate, with a narrow therapeutic index and a wide interindividual variability in the rate of metabolism. This narrow therapeutic range 10–30 mg/L means that levels required for relieving anxiety and producing sedative effects are very close to those associated with toxicity. A phenobarbital overdose can cause central nervous system depression, along with respiratory failure and haemodynamic instability.³ Furthermore, given the reported half life of 5 days, these patients can remain obtunded for some time.⁴

Historical treatment of a barbiturate overdose is based on supportive care, activated charcoal and urinary alkalinisation along with the application of extracorporeal treatments such as charcoal haemoperfusion or haemodialysis. There is, however, a notable paucity of recent evidence supporting one approach over another.

The use of barbiturates in the West has rapidly declined with the advent of benzodiazepines and newer antiepileptic drugs. Barbiturate toxicity results more readily as a result of both the generality of barbiturate binding and the direct opening of the chloride channel by comparison with benzodiazepines. The key clinical feature distinguishing the patient with benzodiazepine intoxication from one with a barbiturate overdose is the ability to quickly antagonise the effect with flumazenil, which competes with the benzodiazepine at the GABA-A receptor. These characteristics of benzodiazepines have contributed to their clinical popularity with the correspondent decline in favour of barbiturates. However, given their continued use elsewhere in the World, the treatment of barbiturate toxicity remains an important topic of interest and one which has had relatively little attention paid to it of late.

CASE PRESENTATION

A 50-year-old woman visiting the UK from Eastern Europe was discovered unconscious after a suspected overdose of 12.5 g of phenobarbital, taken at an unknown point within the preceding 24 h. On presentation to the emergency department, the patient had a Glasgow Coma Scale (GCS) of 3, although she remained haemodynamically stable. The initial phenobarbital level was 143 mg/L (therapeutic range for treatment of epilepsy 10–30 mg/L)—the other toxicology screen was negative. The patient was intubated, ventilated and transferred to intensive care. The patient had initially been prescribed phenobarbital to help with insomnia by her regular doctor in Romania. In light of the patient's long-term barbiturate usage and likely tolerance with potentially enhanced metabolism and clearance, we initially opted for supportive management.

TREATMENT

Following 96 h of supportive care, the patient remained on GCS 3, and despite the incremental reductions in serial levels, her phenobarbital level remained at 115 mg/L. Given the lack of progress in her neurological status, we opted to trial venovenous haemodialysis (dialysate flow 500 mL/min; pump speed 200 mL/min; T 35.5) for a period of 2 h on two separate occasions, in an attempt to enhance clearance of the drug. The patient's phenobarbital levels reduced from 115 to 84 mg/L following the first dialysis and from 78 to 55 mg/L following the second cycle (figure 1).

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Figure 1 Graph demonstrating the elimination of phenobarbital over time. Haemodialysis performed at points indicated by arrows.

OUTCOME AND FOLLOW-UP

At a phenobarbital level of approximately 55 mg/L, the patient spontaneously opened her eyes and was appropriate for extubation within hours. The patient was fit for discharge from critical care within 24 h and went on to make a full recovery. A full psychiatric assessment was made before discharge from hospital.

DISCUSSION

The reported lethal dose of phenobarbital is in the range of 6–10 g,⁵ with concentrations of 80 mg/L reported as fatal.⁶ Our patient ingested a higher dose than that reported as fatal, and was haemodynamically stable, potentially due to the long-term tolerance of the drug. Haemodialysis produced a rapid reduction in the phenobarbital levels and accelerated the clinical recovery of this patient, and has also shown similar success in other cases reported in the literature.

Balme *et al*⁷ presented a case in 1962, whereby a patient presenting with a barbitone level of 60 mg/100 mL was treated with haemodialysis for 8 h and responded similarly, with a return of reflexes and appropriate responses sufficient to be extubated.

Quan and Winter⁸ reported a case of a patient with a phenobarbital level of 163 mg/L on presentation. Similar to our case, the patient showed no improvement for 3 days, and thus was treated with high-flux haemodialysis on two separate days for 2–2.5 h each time, showing remarkable improvement.⁸

Furthermore, Palmer³ reported another case of a comatose patient presenting following a phenobarbital overdose. The patient had a phenobarbital level of 143 µg/mL and failed to respond to repeated doses of activated charcoal.³ However, high-flux dialysis for 4 h resulted in dramatic improvement with the patient responding appropriately by the end of the dialysis session.³

Although cases of phenobarbital overdose treated successfully by haemodialysis have been reported in the literature, there appears to be a lack of consensus regarding whether haemodialysis or haemoperfusion is superior in treating barbiturate overdose. Haemoperfusion was originally deemed to be superior due to its effectiveness in removing highly protein bound drugs, such as phenobarbital which displays 40–60% protein binding.³ However, the premise that haemoperfusion is superior was based on the comparison with low-efficiency dialysers with low blood flow rates.³ The advent of more superior haemodialysis machines calls for a review of the use of haemodialysis as a treatment modality for phenobarbital overdose. Haemodialysis is most effective for drugs with a low molecular weight, high water solubility and small volume of distribution, which is true

of phenobarbital, with volumes of distribution reported at 0.54–0.9 L/kg.^{3 4}

Haemodialysis has been shown in this case, as well as others reported in the literature, to be an effective treatment in high-dose phenobarbital overdose. Plasma clearance of phenobarbital by high-flux haemodialysis has been shown to be 30 times that of hepatic clearance, and 10 times greater than the rate achieved with activated charcoal.⁸ This, combined with the fact that haemodialysis is less expensive and more widely available than haemoperfusion, makes it an appealing choice for this group of patients.⁹

We would support the use of haemodialysis to diminish the prolonged effects of phenobarbital and reduce the length of stay in intensive care units with all the attendant risks of prolonged ventilation such as ventilator-acquired pneumonia together with the increased costs associated with level three critical care.

In summary, this case presents a female patient with a phenobarbital overdose resulting in coma that was treated successfully with two sessions of haemodialysis. We have presented a review of similar cases of successful treatment of phenobarbital overdose with haemodialysis. We conclude that haemodialysis may have a place in reducing the adverse effects of phenobarbital overdose. However, further investigation into the use of haemodialysis as a treatment for phenobarbital overdose is necessary to determine a protocol. What dialysis regime is most effective? Should haemodialysis be used in all cases of phenobarbital overdose, or should there be a specific phenobarbital level to dialyse? Further cases of phenobarbital overdose treated with haemodialysis are required in order to answer these questions.

Learning points

- Phenobarbital remains an important drug that is open to abuse and overdose with significant potential for morbidity and mortality.
- Haemodialysis is widely available in the critical care setting and increases the elimination of phenobarbital.
- Haemodialysis can significantly reduce the length of intubation in patients with overdose.
- Haemodialysis can significantly reduce the length of critical care stay in patients with overdose.

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Competing interests None.

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