Phenobarbital sedation via subcutaneous infusion in a palliative medicine unit: retrospective review

Phenobarbital is a barbiturate medication used clinically for over 100 years for the treatment of seizures, for anaesthesia and more recently for palliative sedation.[1] Its primary mechanism of action is through enhancing the postsynaptic inhibitory activity of Gamma Amminobutyric Acid-A(GABA-A) receptor by permitting more chloride influx, as well as blockade of excitation via glutamate signal. These mechanisms result in hyperpolarised neurons resulting in antiepileptic and sedative properties.[1]

Palliative sedation is the provision of relief of suffering for the terminally ill by the provision of sedative medications, including benzodiazepines and phenothiazine neuroleptics, and in refractory cases, barbiturates. The European Association of Palliative Care framework for sedation states that barbiturates are useful where patients are tolerant to other sedatives due to their differing mechanism of action and as a third-line sedative in the palliative setting if other options have been used.[1] Doses are reported as typically within the 800–1200 mg per 24 hours range via continuous subcutaneous infusion (CSCI), but with significant variability up to 3800 mg/24 hours via CSCI,[1] depending on loading doses required and symptomatic response.

In our centre, phenobarbital is used as a sedative for hyperactive delirium at the end of life, refractory to other sedatives. For this patient group, mean survival in the literature is reported as 24 hours or less.[2] Local practice is to provide a subcutaneous bolus dose of 400 mg phenobarbital, followed by a CSCI starting at or above 2000 mg depending on response to bolus. These doses have evolved from experiential treatment with phenobarbital and a pragmatic response to alleviating distress. This audit aimed to analyse prescription and survival patterns for patients in the terminal phase of life who received phenobarbital per local practice.

METHODS

Pharmacy dispensing books for the ward were reviewed for phenobarbital ampoules in July 2020, with 4 years of records available (2017–2020 inclusive). Ampoule counts dispensed to each patient were matched to the electronic record. Bolus and infusion doses were extracted, and survival time from commencement of phenobarbital to time of death was documented.

RESULTS

Thirty patients were prescribed phenobarbital for sedation at the end of life in the analysis period. Loading doses were either 200 mg (6 patients) or 400 mg (24 patients), with patients receiving 200 mg as loading dose requiring repeat 50% of the time (3/6) and patients receiving 400 mg requiring repeat 46% of the time (11/24). Of patients loaded with phenobarbital, 36% of patients received pro re nata (PRN) only (10) and 64% received infusions (18). Two patients were prescribed infusions but died prior to commencement.

Infusions ranged from 800 mg to 2400 mg on initiation. For patients commenced on lower dose infusions (<1600 mg/24 hours), mean survival was 12 hours post initiation (range 10–16, median 12). For patients commenced on higher dose infusions (2000 mg/24 hours), mean survival was 31 hours (range 16–58 hours, median 29). Maximum infusion dose was 2800mg (1 patient). Overall, 39% of patients receiving infused phenobarbital survived for less than 24 hours post commencement of infusion, the majority received 1600 mg/24 hours or less (4/7).

Cumulative dose of phenobarbital was tallied, including bolus, PRN and infused dose ranging from 200 mg to 7600 mg. As cumulative dose of phenobarbital increased, survival time increased, see figure 1. No adverse effects attributable to phenobarbital were documented in the medical records.

DISCUSSION

Hyperactive delirium at the end of life is distressing for both patients and families, with multiple agents used to relieve this distress, including benzodiazepines, phenothiazines as well as emerging use

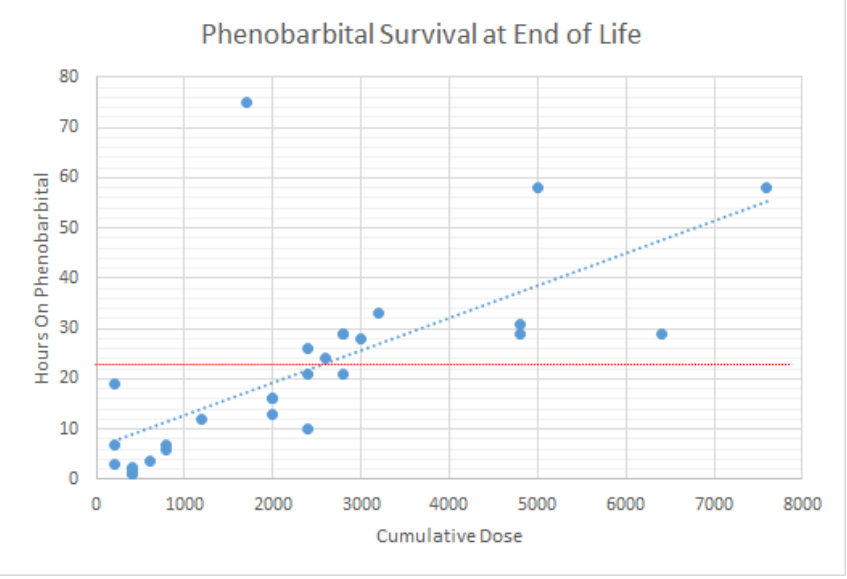

Figure 1 Cumulative dose versus survival for phenobarbital. Red line denotes 24 hours time.

of alpha-2 agonists, for example, dexmedetomidine.[3] Deeper sedation or refractory symptoms however necessitate stronger medication, with phenobarbital recommended for this.[1] Phenobarbital does provide deeper sedation than benzodiazepines or phenothiazines in the terminal phase, with more apparent symptomatic relief.[4]

There are concerns about the use barbiturates, particularly in the climate of expanding euthanasia access, with several jurisdictions using high-dose barbiturates to hasten death in patients requesting euthanasia. However, this audit shows that prescribing phenobarbital in doses up to 2800 mg daily and at high cumulative doses does not appear to result in shortened survival when prescribed for patients suffering from hyperactive delirium at the end of life compared with the literature.[2] Prescription of higher doses appears to have a slight longevity effect, and although this study is limited in the ability to draw any such conclusion, there is evidence that better symptom control in the palliative setting does not hasten death.[5]

Skin necrosis has been reported with the use of phenobarbital as a subcutaneous medication, particularly by bolus dosing.[1] This was not apparent in this patient group, although documentation may have been limited.

LIMITATIONS

Significant limitations exist in analysis of these data. The sample size is small and isolated to an individual centre with limited number of prescribers. The data are retrospective from chart review, which can often be incomplete. There are no head-to-head trials of sedatives at the end of life to determine efficacy, and use of phenobarbital is based on prescriber judgement. Prospective research involving the use of phenobarbital in this setting would prove valuable.

CONCLUSION

Patients treated with phenobarbital for hyperactive delirium at the end of life did not die more rapidly than the reported average in the literature. Phenobarbital appears safe for patients at the end of life requiring deeper sedation.

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REFERENCES

1 Twycross R, Wilcock A, Howard P. *Palliative Care Formulary*. 6 ed. Royal Pharmaceutical Society, 2018.
2 Mercadante S, Intravaia G, Villari P, *et al*. Controlled sedation for refractory symptoms in dying patients. J Pain Symptom Manage 2009;37:771–9.
3 Thomas B, Lo W-SA, Nangati Z, *et al*. Dexmedetomidine for hyperactive delirium at the end of life: an open-label single arm pilot study with dose escalation in adult patients admitted to an inpatient palliative care unit. Palliat Med 2021;35:729–37.
4 Barbato M, Barclay G, Potter J, *et al*. Correlation between observational scales of sedation and comfort and bispectral index scores. J Pain Symptom Manage 2017;54:186–93.
5 Sykes N, Thorns A. The use of opioids and sedatives at the end of life. Lancet Oncol 2003;4:312–8.