

CASE REPORT

Evading Seizures: Phenobarbital Reintroduced as A Multifunctional Approach to End of Life Care

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Abstract

Background: The selected case study aims to evaluate the role of phenobarbital as a drug of choice in end-of-life settings. Phenobarbital is efficacious in management of end-of-life seizures and agitation, can be easily administered via different modes and utilized in various palliative care settings.

Case Presentation: Mrs. X., 90-year-old female with a history of glioblastoma multiforme was a resident of long-term care residing in a palliative care unit. She presented with illness progression which resulted in an increased frequency of generalized tonic-clonic seizures which were managed initially with phenytoin. Due to the advanced stage of the illness and significant decline in the patient's cognitive and physical status, oral route and intravenous access were lost, phenytoin became not an option for seizure control. She was then rotated to subcutaneous phenobarbital, as a result, starting at 30 mg once a day. The dose needed to be titrated up in 15mg increments to achieve adequate seizure control and she stabilized on 60mg of subcutaneous phenobarbital after 2 days.

Discussion/Conclusion: No serious adverse skin reactions were noted with the use of phenobarbital, and it did not abruptly end a patient's life when used at appropriate doses. The sedative properties of phenobarbital had benefited Mrs. X and allowed her to be comfortable approaching end-of-life.

Keywords: Phenobarbital; End-of-Life; Palliative Care; Glioblastoma Multiforme; Seizure Management

Background

Seizures are seen in 13 % of cases in palliative care (PC) and at the end-of-life (EOL) [1]. 25-50% of patients who have brain metastases will develop seizures at the time of diagnosis and will progress in severity with cancer progression [2]. Phenobarbital is a drug from the barbiturate family, most commonly used for its anticonvulsant and sedative properties. It is therefore widely utilized in PC for the management of EOL seizures and agitation. Phenobarbital remains indispensable, it is a reliable, cost-effective drug that has high potency in relieving symptoms patients experience at the EOL. Sometimes overlooked, efficient EOL care can not only provide a peaceful passing with minimal physical and emotional distress but may also have a lasting effect on family members of the deceased. The provided case study demonstrates the role of phenobarbital in symptom management in a patient approaching final days.

Case Presentation

Mrs. X, a 90-year-old Caucasian female with a history of glioblastoma multiforme was a resident of long-term care residing in the PC unit. She had a history of dementia, anxiety, and coronary artery disease. She presented with generalized tonic-clonic seizures as a result of her illness progression which was managed initially with phenytoin. Her blood workup revealed sodium 128mEq/L (normal range sodium: 135-145mEq/L), calcium 3 mg/dL (normal range calcium: 8.5-10.2 mg/dL), fasting glucose 125mg/dL (normal range glucose: 100-125mg/dL) and magnesium 1mg/dL (normal range magnesium: 1.7-2.2 mg/dL). Her medications included hydromorphone, dexamethasone, glycopyrrolate, midazolam and haldol initially, which was later rotated to methotrimeprazine with the disease progression. Due to a significant decline in the patient's cognitive and physical status oral route, and IV access were lost and phenytoin became not an option for seizure control. Midazolam had been attempted with poor response and only partial seizure control. As the frequency of seizure activity increased, she was rotated to subcutaneous phenobarbital with a starting dose of 30mg once a day. The dose was then titrated up in 15 mg increments to achieve adequate seizure control and she stabilized on 60mg of subcutaneous phenobarbital once daily, achieved after 2 days. Unfortunately, her disease continued to progress.

She has developed terminal delirium approaching EOL and had become restless and agitated. Her symptoms were managed well with appropriate titration in 30mg increments of phenobarbital from 60mg up to 120mg subcutaneously once a day to comfort her, which was achieved after 2 days. No local skin reactions were noted. During her stay at the PC unit, she was accompanied by the daughter who noted good symptoms control and reported no further seizures which allowed some quality of time for both of them. Prolonged seizure control with the use of phenobarbital at the EOL for this patient had shown improvement in symptom control and the quality of the remaining life, with no impact on the survival. The sedative properties of phenobarbital had also benefitted Mrs. X and allowed her to be comfortable approaching EOL. She died peacefully 2 weeks later.

Investigations

Mrs. X blood workup revealed sodium 128mEq/L (normal range sodium: 135-145mEq/L), calcium 3mg/dL (normal range calcium: 8.5-10.2mg/dL), fasting glucose 125mg/dL (normal range glucose: 100-125mg/dL) and magnesium 1mg/dL (normal range magnesium: 1.7-2.2mg/dL)

Differential Diagnosis

Based on the presentation of Mrs. X it was apparent that the tonic-clonic seizures were manifestations of the progression of advanced central nervous system malignancies. Mrs. X had a history of glioblastoma multiforme, which has a tendency to cross the corpus callosum contributing to the reoccurrence of seizures. She presented with hyponatremia, hypomagnesemia, and hypocalcemia. Hyponatremia can lead to seizures, usually generalized tonic-clonic and occur if plasma sodium concentrations rapidly decrease to <115mEq/L [3]. It is known that calcium levels between 1.9-2.2mEq/L were shown to produce mild to moderate seizure activity and levels below 1.9mEq/L produced severe seizures [4]. Hypomagnasemia (<1.5mEq/L) is known to be a modulator of seizure activity, which can be caused by poor nutrition or chronic abuse of alcohol. Knowing Mrs. X's history, poor nutrition couldn't be ruled out.

Treatment

Mrs. X presented with tonic-clonic seizures as a result of the progression of her malignancy, Glioblastoma Multiforme and was started on phenytoin as a drug of choice. Blood workup revealed hyponatremia, hypomagnesemia, and hypocalcemia. As the patient's disease advanced, the severity and the frequency of seizure activity had increased, and oral and intravenous access was lost. Phenytoin was discontinued, and subcutaneous phenobarbital was initiated, starting at 30mg once a day with close monitoring every 30 minutes until seizure control was achieved. It took 2 days with gradual titration in 15mg increments of phenobarbital. Seizure frequency and severity were diminishing with every titration up by 15mg increments, which was quantitatively measured by a reduction in the Chalfont score from >100 to <10 [5]. She stabilized on 60mg of phenobarbital on the second day, which allowed her some quality of time with the family. During the maintenance stage while on phenobarbital monitoring occurred every four hours. Unfortunately, her disease continued to progress. She has developed terminal delirium approaching EOL which could be multifactorial and induced by illness progression, medications side effects, or a combination of both. She had become restless and agitated, but her symptoms were managed well with appropriate further titration of phenobarbital up to 120mg given subcutaneously once daily to comfort her as per established goals of care and wishes for EOL management. During the further titration of phenobarbital in 30mg increments from 60mg to 120mg once a day, monitoring was restarted every 30 minutes until symptom control was achieved, which took 2 days. Adequate seizure control with the use of sedative properties of phenobarbital improved the patient's quality of life approaching the final stages, alleviated caregiver distress and had no impact on the survival. No local skin reactions were noted. She died peacefully two weeks later.

Phenytoin and phenobarbital are both effective treatments in partial (focal) and tonic-clonic seizures as well as status epileptics. Phenobarbital facilitates the GABA_A action by increasing the duration of chloride channels in the central nervous system, decreasing neuronal firing, leading to adequate seizure control with minimal adverse effects compared to phenytoin. Additionally, phenobarbital is a long-acting agent, having 10–12 hours of duration, compared to 1–6 hours of midazolam [6]. The longer duration of action allows adequate seizure management with less frequent infusions which helped to minimize the discomfort associated with injection and as a result, improve the quality of remaining life. Mrs. X's condition was terminal, and she was approaching the EOL. Phenobarbital was not only effective in decreasing the reoccurrence and controlling seizures but its sedative properties also helped to achieve comfort and allowed a peaceful death.

Outcome and Follow-up

Incorporating phenobarbital as part of patients daily medical regimen reduced complications associated with EOL care and improved the quality of remaining life. Mrs. X's history was positive for malignancy with central nervous system involvement and decreased seizure threshold. Although other medications were used for symptom control, introducing phenobarbital with its anticonvulsant and sedative properties helped to adequately control seizures and improve EOL experience for both patient and caregiver.

Mrs. X initially experienced generalised tonic-clonic seizures, with no warning, lasting >4 minutes and returning to normal within 2 hours. Initially, seizure severity score was >100 as per Chalfont graded score [5]. Once phenobarbital was administered a quantitative reduction in seizures severity was considered to be <10, which was achieved after 2 days.

Discussion/Conclusion

Mrs. X presented with malignancy and brain involvement. Convulsive episodes could be multifactorial: induced by the brain structure damage and had a systemic origin. Mrs. X had a history of primary tumor, glioblastoma multiforme. 13% of the PC population can develop seizures and phenobarbital is the most commonly used drug in PC settings to control it. Seizures at the EOL occurs most commonly, in 25–50% of the patients who have brain metastases [2]. Subcutaneous phenobarbital in EOL care was approved by the Food and Drug Administration, however, is cautioned due to adverse skin reactions [7], which were not observed in the presented case. A study by Hosgood (2014) reported only 2.9% of patients, from 0.3% of injections, developed mild grade 1 reaction which did not interfere with further administration of phenobarbital [7].

Glioblastoma is a primary central nervous system astrocytoma that has a well-known propensity to cross the corpus callosum. This trait alone introduces the risk of seizure recurrence. Seizures are more commonly associated with tumours found in peripheral brain structures such as the frontal, parietal and temporal lobes of the brain [8]. Typically Glioblastoma begins within the cerebral hemispheres, however, due to its classification as a Grade IV astrocytoma, those structures can be quickly compromised. Central nervous system involvement is especially common in patients suffering from primary small cell lung carcinoma due to immunohistochemical properties of small cell carcinoma to demonstrate chromogranin and synaptophysin positivity. These immunohistochemical markers target neuroendocrine cells and increase the likelihood of seizure development. Epileptogenicity in brain malignancies may be direct effects of the tumour or extracellular cortical hyperactivity [8].

Mrs. X was on hydromorphone, dexamethasone, glycopyrrolate and haldol initially which was later rotated to methotrimeprazine. Among the listed medication, methotrimeprazine has a known propensity of causing epilepsy by lowering the seizure threshold [9]. Hydromorphone has been shown to influence the release of antidiuretic hormone (ADH) causing the retention of water and dilution of sodium. Haldol has been shown to contribute to hyponatremia leading to excessive ADH release. Haldol was subsequently rotated to methotrimeprazine for Mrs. X, as the disease progressed to achieve a better symptom control and comfort level approaching EOL. Medication-induced Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion cannot be ruled out in this setting causing water retention, depleting sodium concentration, and leading to seizures.

According to the BC Palliative Symptom Management Guidelines, the first line therapy for seizure control is Lorazepam [10]. Alternatively, midazolam, phenytoin, or valproic acid may be used. Uncontrollable status epilepticus can be managed with phenobarbital 120mg subcutaneously or intravenously which can be titrated up to control the seizure as per recommended guidelines [11], and as observed in Mrs. X's case. In patients approaching EOL, phenobarbital was introduced as a drug of choice.

Patients that would prefer their setting to be at home during EOL, microenema suspensions delivered via Macy Catheter would be preferable over oral route. The study showed that phenobarbital oral tablets crushed and suspended in water, delivered to the patients using Macy Catheter had a greater efficacy, showed less variability, and higher plasma concentration, and can be easily administered compared to the suppositories which have delayed response and lack of efficacy [12].

Phenobarbital has been used as adjuvant, secondary line of drug for management of seizures, agitations, and sedative purposes like it was observed in the presented case. Current first line drug for Continuous Palliative Sedation Therapy (CPST) is a benzodiazepine [13]. Due its short half-life and low potency the preferred benzodiazepine of choice is midazolam. Midazolam has been used widely and is the first line of drug to treat delirium, agitation and seizures due to its anxiolytic, anticonvulsive and sedative properties, it can be given subcutaneously or intravenously. Mrs. X. experienced severe refractory seizures that were treated with phenobarbital given subcutaneously. Phenobarbital was chosen because it has shown higher efficacy in treating refractory seizures compared to midazolam [14]. Phenobarbital can also be administered intravenously. Using sedative drugs such as midazolam, methotrimeprazine and phenobarbital for sedation, delirium, agitation, restlessness and seizures in the last 7 days of life have shown not to abruptly end a patient's life [15]. Even increasing the dose of phenobarbital in the last hours of life up to 200-500mg/24h to achieve sedation was not associated with overall shortened survival [15]. Although phenobarbital is a second-line drug of choice it can be added to the regimen in cases of suboptimal symptom control. The long half-life of phenobarbital makes rapid titration of it difficult and as a result, the treatment protocol can be subject to change. Level of sedation, level of comfort/discomfort, airway patency and air entry are the primary parameters considered when monitoring patient responsiveness to treatment [16]. These pharmacological variables of phenobarbital allow for eased titration as opposed to the other drugs from the same class.

Often forgotten but floridly relevant, the enhanced quality of life attributed to phenobarbital use in EOL care is not solely benefited by the patient, it also can play a role in alleviating caregiver burden and distress. According to the US National Library of Medicine, caregivers who perceive unmet patient needs reported higher incidences of caregiver burden [17].

A retrospective case study series was conducted by Setla and Pasniciuc (2019) to determine time to death, patient characteristics, and administration protocol in regard to phenobarbital use for EOL care. Their objective was to describe the use of phenobarbital

suppositories in homes for the purpose of sedation, understand patient characteristics of potential users and those in whom suppositories were used, and measure time to death after initiating the phenobarbital suppositories [18]. They found that, of 1675 patients enrolled in hospice over an 18-month period, phenobarbital suppositories were placed in the homes of 90 patients for potential use. Suppositories were initiated in 31 of the 90 patients. Agitated delirium was the major symptom for which suppositories were placed and initiated. Both groups had a greater prevalence of cancer diagnoses than the target population. The mean time to death after initiation of phenobarbital suppositories was 38.8 hours. None of the users were hospitalized [18]. They concluded that the use of compounded phenobarbital suppositories for the purpose of palliative sedation is an alternative for patients and families who desire to remain home despite refractory symptoms [18].

In a study conducted by Allan et al. (2018), the review of the current evidence base provided no standard or optimal dosing regimen of phenobarbital. However, based on the available evidence, a clinical guideline will be produced for use of phenobarbital in intractable agitation at the EOL with an intramuscular loading dose of 200 mg followed by a continuous subcutaneous infusion of 800 mg-1600 mg/24 hrs. Due to the infrequency of this intractable agitation and the use of phenobarbital, sharing and evaluating the guideline at a regional level would facilitate more rapid efficacy assessment and refinement [19]. According to this study, information regarding phenobarbital use for EOL care is underwhelming and clearly should be further explored. The aim of such a study was to determine the optimal dosage of phenobarbital for palliative use, however, just six scholarly articles were referenced in order to support their finding. As pointed out earlier the use of phenobarbital at the EOL offer a substantial benefit which is supported by the presented case vignette and should be further explored.

Statements

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Statement of Ethics

Ethics approval was not required because this case was a vignette. The authors declare this research complies with the guidelines in accordance with the World Medical Association Declaration of Helsinki.

Study approval statement: As a vignette, ethics approval was not required.

Consent to participate statement: As a vignette, consent was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Helen Senderovich was responsible for the conception, design, drafting, clinical revisions and final approval of a version to be published. Helen Senderovich is accountable for all aspects of the published work. Sarah Waicus was responsible for the drafting of the paper, interpretation of the data and critical revisions of the paper. Keisa Mokenela was responsible for the drafting of the paper and critical revisions of the paper.

Data Availability Statement

All data was made available in the manuscript and supplementary material submitted.

References

1. Stirling L, Kurowska A, Tookman A (1999) The Use of Phenobarbitone in the Management of Agitation and Seizures at the End of Life. *J Pain Symptom Manage* 17: 363-8.
2. Tradounsky G (2013) Seizures in palliative care. *Can Fam Physician* 59: 951-5, e401-5.
3. Nardone R, Brigo F, Trinka E (2016) Acute Symptomatic Seizures Caused by Electrolyte Disturbances. *J Clin Neurol* 12: 21-33.
4. Raffaele N, Brigo F, Trinka E (2016) Acute symptomatic seizures caused by electrolyte imbalances. *J Clin Neurol*. 12: 21-33.
5. Duncan JS, Sander JW (1991) The Chalfont Seizure Severity Scale. *J Neurol Neurosurg Psychiatry*. 54: 873-6.
6. Favié LMA, Groenendaal F, van den Broek MPH, Rademaker CMA, de Haan TR, et al. (2019) Phenobarbital, Midazolam Pharmacokinetics, Effectiveness, and Drug-Drug Interaction in Asphyxiated Neonates Undergoing Therapeutic Hypothermia. *Neonatology* 116: 154-62.
7. Hosgood JR, Kimbrel JM, Protus BM, Grauer PA (2014) Evaluation of subcutaneous phenobarbital administration in hospice patients. *Am J Hosp Palliat Care* 33: 209-13.
8. Armstrong TS, Grant R, Gilbert MR, Lee JW, Norden AD (2016) Epilepsy in glioma patients: mechanism, management, and impact of anticonvulsive therapy. *Neuro Oncol* 18: 779-89.
9. Dietz I, Shmitz A, Lampey I, Schulz C (2013) Evidence for the use of Levomepromazine for symptom control in the palliative care setting: a systemic review. *BMC Palliat Care* 12: 2.
10. BC centre for palliative care [Internet]. B.C. inter-professional palliative symptom management guidelines [cited 2021 Oct 16]. Available at: <https://bc-cpc.ca/wp-content/uploads/2018/09/SMGs-interactive-final-Nov-30-compressed.pdf>
11. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, et al. (2013) Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia* 54: 11-27.
12. Lam YF, Lam A, Macy B (2016) Pharmacokinetics of phenobarbital in microenema via macy catheter versus suppository. *J Pain Symptom Manage* 51: 994-1001.
13. Harris N [Internet]. Seizure Management In End-Of-Life Care: Fit for the Future? [cited 2021 Oct 16] Available at: <http://www.swscn.org.uk/wp/wp-content/uploads/2018/02/Seizure-Management-in-End-of-Life-Care.pdf>
14. Legriel S, Brophy GM (2016) Managing Status Epilepticus in the Older Adult. *J Clin Med* 5: 53.
15. Sykes N, Thorns A (2003) Sedative use in the last week of life and the implications for end-of-life decision making. *Arch Intern Med* 163: 341.
16. Kale R, Perucca E (2004) Revisiting phenobarbital for epilepsy. *Bmj* 329: 1199-1200.
17. O'Hara RE, Hull JG, Lyons KD, Marie Bakitas, Mark T Hegel, et al. (2010) Impact on caregiver burden of a patient-focused palliative care intervention for patients with advanced cancer. *Palliat Support Care* 8: 395-404.

18. Setla J, Pasniciuc SV (2019) Home palliative sedation using phenobarbital suppositories: time to death, patient characteristics, and administration protocol. *Am J Hosp Palliat Care* 36: 871-6.

19. Allan R, Curtis M, Morey PJ (2016) A Rapid Evidence Assessment of the Optimal Phenobarbital Dosage Regimen for Management of Intractable Agitation in The Last Days of Life to Produce a Clinical Guideline [cited 2021 Oct 16]. Available from: https://spcare.bmj.com/content/8/Suppl_1/A71.