**Palliative Care Rounds**

**Status Epilepticus in a Hospice Inpatient Setting**

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**Abstract**

Although evidence-based guidelines on the management of status epilepticus in the general population are available, these cannot be readily applied to hospice inpatients. The treatment of status epilepticus in a hospice setting presents many challenges in terms of choice and availability of drugs, route of administration and availability of monitoring facilities. A case report is presented that illustrates the distinct challenges involved in the management of status epilepticus in this setting. Commonly used antiseizure medications are discussed, with emphasis on the potential benefits and drawbacks in a hospice population.

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**Key Words**

Status epilepticus, hospice, anticonvulsant drugs, subcutaneous, intravenous

**Introduction**

Status epilepticus (SE) is a rare but challenging clinical situation in the palliative care setting. Most guidelines for the management of SE recommend the use of agents, all of which are administered intravenously, and advise that neurological, respiratory, and cardiovascular monitoring be available at all stages.\(^1\)\(^-\)\(^3\) Many guidelines also advocate EEG (electroencephalographic) monitoring for refractory SE and availability of the full range of intensive care facilities.

Unfortunately, in a hospice setting these guidelines are not easily applicable:

- Cachexia, dehydration, previous chemotherapy, tumor site, or the use of steroids make intravenous (IV) access difficult, if not impossible.
- Most hospices are not equipped with EEG or cardiac monitoring facilities.
- It may not be appropriate to transfer palliative care patients to an acute hospital for seizure management.

The following case report highlights the challenges of managing SE in a hospice inpatient setting.

**Case Report**

A 30-year-old woman with stage three olfactory neuroblastoma was admitted to the hospice for symptom control. She had received whole brain radiotherapy one month prior to
admission for progression of brain metastases. She had no prior history of seizures but had been commenced on prophylactic phenytoin at least 12 months previously.

She had developed intermittent shaking of her right arm and leg and had become increasingly unsteady on her feet over a few days prior to admission. In an attempt to alleviate her symptoms, her dose of dexamethasone had been increased from 4 mg to 8 mg daily three days previously. She also had been commenced on a syringe driver containing 10 mg midazolam, 60 mg diamorphine, and 30 mg metoclopramide per 24 hours subcutaneously (SC) 24 hours prior to admission because she was having difficulty taking oral medication regularly. Apart from dexamethasone and phenytoin, her other oral medications included acetaminophen (paracetamol), lansoprazole, amitriptyline, and codanthramer, all of which she had been taking regularly for some time.

On the day of admission, the intermittent tremors and restlessness were felt to be metoclopramide-induced akathisia and her antiemetic was changed to cyclizine. The midazolam was increased to 15 mg per 24 hours. The dose of diamorphine remained the same. At that stage, physical examination revealed her to be hypertonic and hyperreflexic, with slightly reduced power (4+/5) in her right arm and leg, which was longstanding. She had a Babinski sign on the right.

On the second day of her admission, the clinical picture changed in that she was noted to have altered consciousness and marked continual jerking of her right arm and leg. Her phenytoin level was 4 mg/L (local laboratory therapeutic range 10–20 mg/L). Apart from a slightly elevated white count (presumed secondary to steroids as there was no obvious source of infection), her blood tests, including glucose, adjusted calcium, and renal and liver function, were within normal limits.

At this stage, the midazolam was increased to 30 mg SC over 24 hours. The seizures and her conscious level improved temporarily. Later that evening, the midazolam dose was reviewed and increased to 50 mg over 24 hours SC because of increasing right-sided twitching. Over the next four hours, the agitation and limb jerking became even more pronounced despite an extra 25 mg midazolam as SC or buccal bolus doses. Over this period, she was also given a total of 500 mg phenobarbitone SC as bolus doses of 100 mg and 200 mg at a time, with little effect.

Venous access was extremely difficult but was eventually obtained. She responded to two 5 mg midazolam IV boluses and an IV midazolam infusion was commenced at an initial rate of 2.5 mg per hour. This was titrated to 10 mg per hour over the next 12 hours. At each dose increment, the seizures appeared to respond for a short period. However, even at the higher doses, she needed at least one further bolus of 10 mg midazolam IV per hour. While the IV midazolam infusion was running, a phenobarbitone infusion 1200 mg SC over 24 hours was commenced. This continued to infuse over a period of 18 hours. It became clear, however, that the combination of midazolam IV and phenobarbitone SC was not fully effective in controlling the seizures and the midazolam infusion was discontinued.

After consultation with an anesthesia colleague, she received an IV bolus of 50 mg phenobarbitone and the SC phenobarbitone infusion was converted to phenobarbitone IV 48 mg per hour. It was decided not to administer an IV loading dose of phenobarbitone because she had been given previous SC doses and there was concern that an additional IV loading dose may lead to circulatory collapse. The dose of IV phenobarbitone was increased after three hours to 72 mg per hour. This halted the seizures for about five hours.

On the third day of her admission, the seizures worsened again. A second IV line was established, again with considerable difficulty, and her seizures responded well to three boluses of 1 mg clonazepam IV. A continuous IV infusion of clonazepam 1 mg per hour was commenced. The IV phenobarbitone infusion was continued. A combination of clonazepam 1 mg/hour IV and phenobarbitone 72 mg/hour IV kept her seizure-free and comfortable until her death 12 hours later.

Her level of consciousness fluctuated considerably during her admission, with periods of alertness and confused speech alternating with episodes of reduced consciousness. During the final 24 hours, her level of consciousness deteriorated significantly. It was noted that her respiratory rate was stable for the entire treatment period and only fell below 16 breaths per minute just before she died.
Initially, when it became apparent that her seizures were very difficult to control (even prior to the first bolus dose of SC phenobarbital on the second day of admission), we considered transferring the patient to an acute hospital for medical management. It had been clear from the day of her admission to the hospice that her disease was extensive and that her prognosis from her cancer was very poor. After detailed discussion with the patient’s family, her oncology team and the local intensive care unit, it was felt that transfer to an acute medical setting would not be in her best interests. We discussed every change in medication in detail with her family, including an explanation about the lack of monitoring and respiratory support facilities in the hospice. Her family’s wishes were that she be kept comfortable in the hospice.

**Discussion**

SE is the term used to describe any abnormal, persistent seizure activity. Various definitions of SE exist, many of which differ according to the duration of the seizure. A useful clinical definition is that of continuous seizures lasting at least five minutes or at least two discrete seizures between which there is incomplete recovery of consciousness. SE may present clinically in a number of ways: long-lasting seizures, repeated generalized convulsive seizures with no recovery between seizures, nonconvulsive seizures associated with altered consciousness, and repetitive partial seizures that are not associated with alteration of consciousness.

Refractory SE is that which does not respond to first or second line treatment. Refractory SE occurs in approximately 30% of cases of SE.

The absolute annual incidence of SE in the general population has been shown to be 41 cases per 100,000 per year. This figure is possibly an underestimation because of the inability to document all cases. The incidence of SE in the palliative care population is at present unknown.

**Treatment of SE in a Hospice Inpatient Setting**

The overall aim of palliative care is to provide relief from distressing symptoms and to enhance quality of life. In accordance with this, the aim of treatment of SE in an inpatient hospice setting may vary from patient to patient. This may range from treatment with a view to restoring preseizure functioning to treatment with a view to maintaining the comfort and dignity of the patient during the terminal phase. The main factors that influence the aims and goals of treatment of SE in a hospice inpatient setting are the diagnosis and prognosis of the patient.

SE is associated with an overall mortality of 21%–33% in the general population. It is assumed that the mortality of SE in the palliative care population is higher than that in the general population but as yet there are no available figures to support this. The predominant factor influencing outcome after SE is the underlying cause/disease. Thus, in patients with advanced disease and a poor prognosis (as in the case discussed), SE may be a terminal event. Seizures associated with disorders of the central nervous system are generally more difficult to control and are associated with a high mortality.

Outcome after SE also is determined by the duration of the episode. After approximately 30–60 minutes of continuous seizures, the protective compensatory mechanisms, which exist in the early stages of SE, fail and there is a progressive increase in the risk of cerebral damage. In the general population, only 29% of patients return to their premorbid functional baseline after an episode of SE. In a patient with advanced cancer and brain metastases, this figure would be expected to be much lower.

Transfer of the patient from an inpatient hospice setting to an acute medical setting may facilitate more extensive monitoring and support for the patient, which may not be available in the hospice. The decision to transfer or not should be determined by an evaluation of the potential expected benefit to the patient. Reversibility is a key issue and may be considered if the episode of SE is thought to be due to withdrawal of pre-existing antiepileptic medication, if the patient has a good prognosis in terms of their underlying disease and the goal is control of seizures with functional return, or if the episode is thought to be due to an intercurrent reversible condition, for example, infection/metabolic disturbance. Such patients would benefit from interventions
such as EEG monitoring to verify the course of the episode and the response to treatment. As EEG monitoring is not available in most hospices, it may be appropriate to transfer such patients to an acute medical setting. Similarly, patients who may have a potentially better outcome after an episode of SE may benefit from nutritional and fluid support during a prolonged treatment period. In the case of a patient for whom the episode of SE is probably a terminal event, such interventions would be futile and burdensome.

The views and wishes of the patient and family should be sought wherever possible, particularly if there have been previous episodes and advance care planning for the next episode is feasible.

In the treatment of SE in an inpatient hospice setting, medications may be used that are outside the recommended dose range, due to difficulty in controlling seizures and lack of evidence of the use of these medications in this patient population. Similarly in this setting, these agents are often used without availability of the generally recommended monitoring. The management plan of SE in an inpatient hospice setting should include a plan of action for management of acute anticonvulsant toxicity. Such a management plan will be influenced by the expected outcome/prognosis of the patient and the perceived reversibility of the seizure event. Thus, a patient who has a good prognosis and for whom a return to preseizure function is expected, acute cardiopulmonary compromise would necessitate cardiopulmonary support, probably with transfer to an acute medical setting. On the other hand, if the episode of SE is thought to be a terminal event, it may be difficult to assess whether the deterioration in cardiopulmonary function is due to the antiseizure medication or to the fact that the patient is dying, and such patients may not benefit from cardiopulmonary resuscitation.

The potential side effects and benefits of medications used in the treatment of SE should be assessed and discussed with the patient (if possible), family, and medical and nursing staff. An in-depth knowledge of the effects and mechanisms of action of these agents and careful incremental dose titration according to response is essential to minimize potential adverse reactions. The decision to use agents that are off-license and off-label should be made with serious consideration of alternatives and as part of a multidisciplinary team.

**Medications for Generalized Convulsive SE**

The following discussion concerns medications that are primarily used for the management of generalized convulsive SE, as occurred in our patient. An overview of the management of nonconvulsive SE may be found elsewhere. The most commonly used antiseizure medications are discussed, with particular emphasis on those used and available in a hospice setting and also on alternative routes of administration. It should be noted that much of the evidence for use of these medications in a hospice setting is derived from studies in a nonhospice, acute medical setting.

Tables 1 and 2 summarize the routes of administration, and the recommended and reported doses of drugs commonly used in SE.

**Benzodiazepines.** Benzodiazepines are the preferred initial treatment of SE because of their ability to enter cerebral tissues rapidly. All may be associated with respiratory depression and cardiovascular compromise. One of the most useful distinctions among the different benzodiazepines in the management of SE is their duration of action. This is related in part to their affinity for receptors in the brain. Diazepam has the shortest duration of action of less than two hours, with midazolam acting for three to four hours, clonazepam for 24 hours, and lorazepam for up to 72 hours. There is a risk of accumulation with all benzodiazepines when administered repeatedly.

In the community setting, rectal diazepam is often recommended as an effective first-line treatment of SE. It has been shown repeatedly to be more effective than placebo in the management of acute repetitive seizures. If the rectal preparation of diazepam is not available, the IV preparation may be infused rectally via a syringe. If the IV route is available, longer acting benzodiazepines, for example, lorazepam or clonazepam are considered to be more effective.

Intravenous lorazepam is considered by many sources to be the first-line treatment of choice in SE in the general population. A recent Cochrane review concluded that lorazepam is superior to diazepam or phenytoin
alone in the treatment of SE. The use of lorazepam is limited in the hospice setting, however, because it is best administered IV, although anecdotally it has been used sublingually for single isolated seizures in palliative care patients.

The use of clonazepam for SE has not been extensively studied in clinical trials. One study comparing boluses of IV lorazepam to IV clonazepam demonstrated greater EEG improvement with lorazepam but more complete resolution of clinical symptoms with clonazepam. In the hospice setting, clonazepam would appear to be a suitable alternative to lorazepam because it can be administered both IV and SC and has a suitably long duration of action. Clonazepam is compatible with many drugs in a syringe driver.

### Table 1

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Route of Administration</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>PR</td>
<td>10–20 mg; May be repeated after 15 minutes</td>
<td>May cause rectal burning/irritation for up to 15 minutes after administration</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>10 mg over 2–5 minutes; May be repeated once after 15 minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>Bolus: 0.5–1.0 mg/kg usually 4 mg, at a rate of 2 mg/minute; May be repeated once after 20 minutes</td>
<td>Not recommended as poor absorption</td>
</tr>
<tr>
<td></td>
<td>SL</td>
<td>Similar doses to IV</td>
<td>Anecdotal evidence</td>
</tr>
<tr>
<td></td>
<td>Intranasally</td>
<td>Similar doses to IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>Not recommended as slow absorption</td>
<td>Non-PVC tubing recommended to avoid sorption</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>IV</td>
<td>Bolus: 1 mg at a rate of &lt;2 mg/minute; Infusion: 2–10 mg over 24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>Similar doses to IV</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>IV</td>
<td>Bolus: 0.1–0.3 mg/kg bolus; Infusion: 0.05–0.4 mg/kg/hour; Infusion doses up to 0.6 mg/kg/hour reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>Similar doses to IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Buccal</td>
<td>10 mg bolus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intranasal</td>
<td>0.2 mg/kg bolus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>0.2–0.3 mg/kg</td>
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**Table 2**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Route of Administration</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>IV</td>
<td>Infusion: 15–20 mg/kg at rate &lt;50 mg/minute</td>
<td>Not suitable as tissue irritant/ unpredictable absorption</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>IV</td>
<td>Bolus: 15 mg phenytoin equivalents/kg at a rate &lt;100–150 mg/minute; Maintenance dose: 4–5 mg/kg/24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>IV</td>
<td>Bolus loading dose: 10–20 mg/kg at a rate &lt;100 mg/minute; Maintenance: 1–4 mg/kg/day; Higher doses have been described: 30–120 mg/kg/24 hours</td>
<td>Incompatible with most drugs in syringe driver except diamorphine and hyoscine hydrobromide</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>Bolus loading dose: 100–200 mg; Infusion: 600–2400 mg/24 hours Some authors recommend lower doses 100–200 mg/24 hours</td>
<td></td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>IV</td>
<td>Bolus: 10–20 mg/kg at a rate &lt;25 mg/minute; Infusion: 0.5–3 mg/kg/hour</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>IV</td>
<td>Bolus: 1 mg/kg; Infusion: 1–15 mg/kg/hour</td>
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</table>

PR = rectal; IV = intravenous; IM = intramuscular; SL = sublingual; SC = subcutaneous.
clonazepam to PVC tubing has been demonstrated, both using the IV and SC routes.\textsuperscript{32} Midazolam is also widely used in both the general population and in palliative care patients. Midazolam coma has been used to treat refractory SE in children\textsuperscript{23} and high doses of midazolam have been shown to control seizures that have not responded to traditional agents.\textsuperscript{24} It has been shown that prolongation of the half-life may occur after sustained infusion, thereby increasing the risk of adverse effects.\textsuperscript{25} Conversely, tachyphylaxis may occur with prolonged administration.\textsuperscript{26} Midazolam may be administered IV, SC, intramuscularly (IM), intranasally, and buccally.

Other Drugs. Intravenous phenytoin controls up to 91\% of cases of SE\textsuperscript{5} but is associated with heart failure and hypotension in 28\%–50\% of patients.\textsuperscript{12} Phenytoin is not commonly used in a hospice setting because it is limited to IV administration. A double-blind, randomized, controlled trial showed no significant difference in efficacy of IV phenobarbitone and IV phenytoin in the management of adults with generalized convulsive SE.\textsuperscript{17} This suggests that even if IV access is available, phenobarbitone, which also may be administered SC and which is more commonly available in a hospice setting, may be a more appropriate alternative for palliative care inpatients.

Fosphenytoin is a prodrug of phenytoin. IV or intramuscular (IM) administration results in rapid absorption.\textsuperscript{27,28} Anecdotally, fosphenytoin has been used SC in a hospice setting.

Fosphenytoin doses are expressed as phenytoin equivalents. IM fosphenytoin has been shown to have comparable efficacy to oral phenytoin.\textsuperscript{29} Hypotensive and cardiac side effects are similar between phenytoin and fosphenytoin.\textsuperscript{12} This drug recently has fallen out of favor, however, because of reports of cardiac arrest and because of its cost.\textsuperscript{50} The recommended and reported doses of phenytoin and fosphenytoin in SE are summarized in Table 2.

Phenobarbitone, a barbiturate with a very long half-life, has been used to control seizures and agitation in palliative care patients.\textsuperscript{31} It may be administered IV or SC, but can be an irritant to the skin. Although some clinical effect may be apparent within minutes of administration, maximal clinical benefit is not immediate due to delay in entry of the drug into the central nervous system.\textsuperscript{32} It is important to note that phenobarbitone is metabolized by the cytochrome P450 system and is a potent enzyme inducer.\textsuperscript{35} Acute drug tolerance has been reported.\textsuperscript{34} There are concerns that when administered in conjunction with benzodiazepines there may be an increased risk of respiratory depression.\textsuperscript{32} The reported dosing range of phenobarbitone is variable. Most reports in the literature describe the administration of phenobarbitone as intermittent IV boluses, given 30–60 minutes apart in order to allow penetration of the central nervous system.\textsuperscript{34} This approach is not always appropriate for the palliative care patient, however; thus, an IV infusion was commenced in our case patient. In most cases, the dose of phenobarbitone is titrated in an incremental fashion according to effect. There have been recent concerns that phenobarbitone is no longer available in some countries.

Another barbiturate used in the management of SE is pentobarbital. This metabolite of thiopental is associated with a significant risk of hypotension, especially in elderly patients.\textsuperscript{35} The use of propofol has been described in refractory SE.\textsuperscript{36,37} It may only be administered IV. A review of propofol for resistant SE concludes that overall the evidence for using propofol in SE is weak and is based on small trials and case series.\textsuperscript{36} A systematic review comparing the efficacy of propofol, pentobarbitone, and midazolam in the management of refractory SE did not demonstrate any efficacy advantage of propofol over the other two agents.\textsuperscript{39} The potential advantage of propofol as an antiseizure medication is its rapid onset of action. Unfortunately, this is thought by many to be outweighed by its many potential dangers.\textsuperscript{40} Propofol has the potential to induce seizures at doses lower than those recommended or when abruptly discontinued\textsuperscript{41} and it is associated with an increased mortality rate.\textsuperscript{40}

Conclusion

There is little evidence to underpin the management of SE in hospice inpatients and, therefore, clinical practice is derived from evidence in other patient populations, for example, pediatrics, and anecdotal data. The ideal antiseizure medication in a palliative care setting is appropriate for SC as well as
IV administration, safe with few side effects (or with adverse effects that are readily diagnosed and easily rectified), readily available, cheap and with a long shelf life.

The current agents used in the management of SE are benzodiazepines, phenytoin, barbiturates, and anesthetic agents. None of these agents fulfills all of the above criteria. Commonly used drugs in a hospice setting that are useful in the management of SE include benzodiazepines (midazolam and clonazepam) and barbiturates (phenobarbitone). IV access is not advocated by many to be the optimal route of drug administration in the dying patient because of its invasive nature. However, in the case of SE, we recommend that it is strongly considered, especially if alternative routes are not successful, as the distress from repeated seizures must surely outweigh the distress of obtaining IV access.

Our case illustrates the challenges and difficulties in managing SE in a setting where monitoring facilities may not be available and where IV access may not be possible. This case also demonstrates, however, that in difficult or refractory cases of SE, approaches to improving drug efficacy may include:

- Switching to an alternative benzodiazepine, especially to one with a longer duration of action.
- Using combination therapy from two different drug classes (although caution with side effects).
- Switching the route of administration, in this case from SC to IV.

Further research is needed in the hospice setting to establish evidence-based guidelines, so that this distressing clinical scenario is managed effectively and efficiently, thus minimizing anxiety and physical discomfort among patients, relatives, and staff.

Acknowledgments

The authors would like to thank the family of the above patient who gave permission for this case to be presented.

References


