

SEIZURE MANAGEMENT IN CHILDREN REQUIRING PALLIATIVE CARE – A REVIEW OF CURRENT PRACTICE

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Abstract

Aim: Controlling seizures in children approaching death can be difficult, and there is a limited evidence base to guide best practice. We compared current practice against the guidance for seizure management produced by the Association of Paediatric Palliative Medicine (APPM).

Methods: Retrospective case note review of episodes of challenging seizure management in children receiving end-of-life care over a ten year period (2006-2015) in the southwest region of England.

Results: We reviewed 19 admissions, in 18 individuals. Six (33%) had a malignancy, nine (50%) had a progressive neurodegenerative condition, and three (17%) had a static neurological condition with associated epilepsy. Thirteen (72%) died in their local hospice, four (22%) at home, and one (6%) in hospital. 17/19 episodes involved the use of subcutaneous or intravenous midazolam infusion, for a mean of 11 days (range 3-27). There was a wide range of starting doses of midazolam, and 9/17 (53%) received final doses in excess of current dose recommendations. Six individuals received subcutaneous phenobarbital infusions, with four of these (67%) receiving final doses in excess of current dose recommendations. Plans for adjustments of infusion rates, maximal doses, or alternative approaches should treatment fail were inconsistent or absent. In 16/18 (88%) cases seizures were successfully controlled prior to the day of the child's death. Staff found the experience of managing seizures at end-of-life challenging and stressful.

Conclusions: Pharmacological approaches to seizure management in end-of-life care are variable, often exceeding APPM dose recommendations. Despite this, safe and effective seizure control was possible in all settings.

Many children with life-limiting illness have underlying neurodegenerative or neuro-metabolic conditions, or structural CNS deformities¹, associated with a tendency for seizures. The ability to control seizures is important, not simply because they may present as an emergency as death approaches, but also because uncontrolled seizing is not part of the peaceful death that parents and professionals wish to achieve for these children. Unfortunately, as a child's health deteriorates, maintaining good seizure control becomes increasingly challenging. This may occur due to progression of the underlying condition and associated co-morbidities; concomitant problems with swallowing, absorbing, or metabolising usual medications; and difficulties in obtaining, and maintaining, venous access²⁻⁴. Over recent years, paediatricians involved with the management of seizures have become increasingly aware that seizure management strategies used in acute paediatrics, which are predicated upon vigorous use of interventions such as IV medication, sedation, intubation and ventilation, may not be appropriate for children with a life-limiting illness who require end-of-life care. Progressive deterioration, and the recognition that death is approaching, provides the opportunity to plan for a child and family's needs in advance, and to develop individual management plans based on the child's best interests⁵.

Case examples shared within our regional children's palliative care network meetings suggested wide variability in approaches to seizure management in the palliative care setting, and uncertainty amongst clinicians about the best way to manage these scenarios and support the affected children and families. In response to these concerns, we surveyed specialist and generalist paediatricians, and practitioners in children's palliative care teams across the region to ascertain the levels of concern. This web-based survey took place in August/September 2015, attracted 57 responses, and confirmed that although 92% of respondents felt that they would be asked to manage or advise on seizure management in their patients as they approached end-of-life care, only 26.5% felt usually confident to do this. In light of these findings, we reviewed the literature searching for guidance appropriate to this situation, and sought permission from survey respondents to review their cases

anonymously in order to gain more insight into the challenges faced when managing seizures in these situations. This paper reports these findings.

Literature review

Sources of peer-reviewed publications included Medline (OVID), NHS Evidence (AMED, EMBASE, HMIC, BNI, Medline, Psychinfo, CINAHL, HEALTH BUSINESS ELITE), and Cochrane Database. These were supplemented by broad internet searches for guidelines and protocols, and focussed searches of repositories of relevant information such as PalliativeDrugs.com and the APPM Master Formulary. Two individuals (NH and KB) searched independently and amalgamated relevant results. The bibliographies and references of these were hand-searched for completeness. (See appendix for search terms).

Studies for inclusion considered the age range (0-mid-twenties), with refractory seizure management in a palliative care scenario, in any setting. We looked particularly for information about details of pharmacological management such as prevention strategies, drugs used (and whether they were successful or not), dose increments, arrangements for investigation or monitoring, and practical advice on drug administration and patient care. As RCTs did not exist, we considered reviews, case reports, and best practice recommendations.

Papers were excluded if they described treatment for older adult cancer patients only, as the aetiology and management of seizures in this situation is quite different from the majority of younger patients⁶. We also excluded papers reporting interventions that would not be appropriate in an end-of-life situation (such as palliative epilepsy surgery).

The literature review found that relevant, peer-reviewed publications relating to seizure management in end-of-life care in children or young people are rare; most were single case studies⁷⁻¹⁰ rather than a comparative evaluation of a series of patients &/or interventions, and they were generally lacking in detail about seizure management. Review of pharmacology papers found many

relating to challenges in administration of antiepileptic drugs, but not necessarily within the constraints of a palliative care situation¹¹⁻¹³. Review of the grey literature found a variety of clinical guidelines^{14,15} for seizure management in end-of-life care for children, but many of these did not include an evidence base for their recommendations.

Case Note Review

The survey of colleagues across the region confirmed that the majority would consult the guidance produced by the Association of Paediatric Palliative Medicine when seeking advice about pharmacological management of seizures in end-of-life care¹⁶, so this was used as the reference point for an audit of current prescribing practice. This guidance recommends the use of one or two doses of benzodiazepines such as buccal midazolam or rectal diazepam in the first instance, followed by rectal paraldehyde should benzodiazepines fail. If this too is unsuccessful, parenteral midazolam via subcutaneous or IV infusion, and phenobarbital (oral if tolerated, or parenteral) are the mainstays of seizure management in situations where “standard care”, involving IV antiepileptic drugs and ultimately thiopentone sedation with ventilation on PICU, is not felt to be appropriate for the child’s current circumstances.

We performed a manual retrospective review of case notes about episodes of challenging seizure management in children receiving end-of-life care. Cases were included if they involved children or young people aged between 3 months and 25 years, who were receiving medical care for a known life-limiting illness, where the typical emergency approach to the management of seizures or status epilepticus was limited by an advanced care plan or agreed best-interests decision. We looked for cases where a child had died in the preceding 10 years (between 1/1/2006 and 31/12/2015), and the clinicians reported difficulties controlling epilepsy during palliative or end-of-life care. The review took place between October 2015 and February 2016.

Cases were identified by respondents to the survey described above, and purposively, by targeted approaches to service providers likely to be involved in supporting children in this situation. This

included the specialist paediatric palliative care and paediatric neurology teams, local children's hospices, and district general hospitals across the region. In addition, the controlled drug registers in the hospices were examined, looking for names of children who had received parenteral phenobarbital or midazolam, to identify children who had not been recalled through other methods.

Case notes from the clinical team providing care at the time the child died were reviewed by the lead clinician or named nurse involved, or by members of the project team, in both circumstances using an agreed proforma. Data collection included background information about the child, pre-existing medical and pharmacological history, and the details of the final admission or episode of care, with a particular focus on prescription charts and contemporaneous medical and nursing instructions about seizure management. Where possible, notes from the other sources (eg local hospital or regional specialist team) were inspected to ensure as full a picture as possible. If the notes reviewer was not directly involved in the care of the child, the project team member contacted the clinicians in person or by email to ensure that the details recorded on the proforma were an accurate reflection of events, in order to minimise interpretation bias. Data were collated and processed using Excel™, and results analysed with input from all project members.

The ethics advisory service for United Hospitals Bristol Foundation Trust was approached and advised that the project was an audit, not research, and did not require approval from the Ethics committee. Audit governance was provided by United Hospitals Bristol NHS Foundation Trust Clinical Audit department, ref UHB 4199.

Results

Twenty-two cases were identified, but 4 were excluded as they died from other causes such as chest infections or planned extubation, without exacerbation or complications of epilepsy during their end-of-life care. The remaining eighteen cases included one who was admitted in status epilepticus with death anticipated, but recovered and was eventually discharged home. This child was

readmitted some months later in similar circumstances and then died, so in total 19 episodes of care were reviewed.

The characteristics of the 18 cases are outlined in Table 1. For many children care had been palliative since the time of their diagnosis, and the duration of their end-of-life care ranged from 4 days to 64 days, with a median of 2 weeks. There was documentary evidence of discussions about treatment decisions and care planning before the deaths of all the children. Of these, 16 were in a format such as the Wishes document¹⁷ which could be distributed to all involved healthcare professionals. In 10/16 cases these documents had been updated within the last month of the child's life.

Table 1. Patient Characteristics of Audit Cases

Descriptor	Range	Comments
Age	1-4 years = 5 5-9 years = 5 10-14 years = 6 15+ years = 2	Mean age 8.9 years Range 1-18 years at death.
Year of Death	2006 & 2007 = 1 2008 & 2009 = 6 2010 & 2011 = 1 2012 & 2013 = 5 2014 & 2015 = 5	
Diagnosis	CNS malignancy = 6	Eg Primary CNS tumour, CNS metastases
	Progressive neurological = 9	Eg Batten's disease, mucopolysaccharidoses, leucodystrophies
	Static neurological = 3	Eg Cerebral palsy, microcephaly with epilepsy
Place of Death	Hospital = 1 Home = 4 Hospice = 13	Hospice numbers include 2 initially supported at home, and 1 initially treated in hospital, who were transferred to hospice for management of subcutaneous infusions.

Most children received their usual antiepileptic drugs by mouth or gastrostomy until shortly before they died. Fifteen of the eighteen encountered difficulties with drug administration during the final two weeks of life, either due to vomiting (3), an unsafe swallow (5) or gut dysmotility and poor absorption (7). In 5/18 episodes the child's usual antiepileptic drugs were discontinued in the final

week of life, either because they were not available in a format that could be administered (eg no parenteral, rectal, buccal or topical alternative) or because enteral administration was clearly ineffective. Seizures typically re-appeared 2-3 days later, sometimes taking many hours to control. In all the cases continuous infusions were needed at some point prior to death in order to maintain symptom control; in 3 cases these were IV infusions via central venous devices, and the remainder were subcutaneous infusions.

We reviewed the use of antiepileptic drugs to treat breakthrough seizures or status epilepticus in 19 episodes of care, as documented in table 2 and illustrated in figures 1 and 2.

Table 2. Pharmacological interventions for seizure management in EOL care.

Intervention	Drug(s)	# cases who had it prescribed	# cases delivered to child	Dose range	comments
First line Benzo-diazepines	Diazepam pr	5/19	5/19	10 mg daily, up to 80mg/day	1 on this long-term, 3 children on recommended "standard" doses. 1 on 20-80mg/day ie up to 4 x standard dose.
	midazolam buccal	13/19	13/19	2.5-10mg, according to age	Appropriate dosing in 10/13 episodes. 3 cases had unusually large doses (ie up to 5x daily).
2 nd line	Paraldehyde pr	11/19	5/19	20-40mg	Written up but not given in 6/11 cases, but not clear why. 3/5 used this regularly.
3 rd line	Midazolam infusion (IV or subcutaneous)	18/19	17/19	Starting doses (data available for 16/17 cases) between 10-150 micrograms/kg/hour (fig 1) Final doses between 30-360mg/day, or 36-694 micrograms/kg/hour (fig 2)	Duration of infusion 3-27 days (mean 11 days). All 4 home deaths involved s/c midazolam infusions, for 3,7,14, & 27 days. Median start dose 38 mcg/kg/hour. Median final dose 142 mcg/kg/hour. 9/17 final doses were above 100mg/24 hours, as recommended 2011 APPM formulary guideline doses. 2/17 exceeded 300mcg/kg/hour as recommended in BNFC 2014/15.

4 th line	Phenobarbital infusion (IV or subcutaneous)	10/19	6/19	10 mg/kg/day, up to 35 mg/kg/day (1800 mg total)	Duration of infusion 2-12 days (mean 7.3 days). Usually effective within 24-48 hours. Loading doses required in 5/6, but only given correctly in 1/5 cases. Final doses exceed recommended APPM and BNFC guidelines of 10mg/kg/day, or 600mg total, in 4/6 cases.
others	Lorazepam IV	2/19	1/19	0.05mg/kg, then 0.12mg/kg	No beneficial effect seen, so discontinued.
	Phenytoin IV	0			1 child was on this whilst in hospital, long-term. It was not used in management of any episode of status in EOL care.
comments	Levetiracetam, Clobazam, and Clonazepam were not used as part of emergency or parenteral seizure management in end-of-life care in this group of patients.				

Whilst reviewing the pharmacological interventions, we searched for written advice on plans for treatment escalation, incremental dose increases, or maximal dose limits, particularly when using infusions of midazolam and phenobarbital for sedation. There were clear plans for treatment escalation in 12/18 cases, with the remainder described as “vague” or only partially applicable (eg advice for hospice/hospital management but not community management, or for some drugs but not others). When infusions were running, 15/18 included instructions on dose increments, usually 25% of the previous rate, but few had much detail included such as what observations should be done, what time intervals allowed, or what findings should suggest an increase or decrease in the infusion rate. In three cases, infusions had no instructions for management beyond the preliminary prescribed dose. Maximal doses were identified for only 8/18 cases (6/13 hospice deaths, and 2/4 home deaths). The authors note that the maximal dose recommendations for parenteral midazolam in the APPM formulary have changed over the timeframe of this study, but the final doses were in excess of the recommendations of the 2011 edition in 9/17 cases. Recommended maximal doses were reduced in the most recent (2017) version of the formulary.

Despite the risks of apnoea with large doses of benzodiazepines, this did not appear to be an issue with the use of subcutaneous infusions in this cohort. There were no instances reported where over sedation led to the consideration of flumazenil or physical interventions to support respiration.

One child on very high concentrations of midazolam suffered skin irritation around the subcutaneous cannula sites, requiring relocation of the infusion on a daily basis. There were no reported instances of skin irritation around the phenobarbital infusion sites.

All of these children had other medications for symptom control running alongside their antiepileptic regime. These frequently included opiates for pain management, and a variety of anti-emetics. On occasions, the practical aspects of drug administration added to the complexity of seizure management: one patient had 4 drugs in one syringe driver, meaning that changes in the rate of flow adjusted multiple drug doses simultaneously. Two children received three separate subcutaneous infusions for their symptom control (for midazolam, diamorphine, levomepromazine, ondansetron and phenobarbital) which required considerable nursing support and multiple needle access points.

Fourteen of the eighteen children experienced seizures in their final two weeks of life, and an additional child had abnormal movements which may have been seizure activity. One child had problematic seizures the day before death, but these were brought under control for her final 6 hours. Another had had intermittent recurrent seizures for a few weeks before he died, but had a final seizure only 10 minutes before death. In 16/18 cases seizures were successfully prevented or controlled prior to the day of the child's death, which was described as "peaceful" by staff in 10/18 cases.

The audit forms were returned with covering letters or comments which illuminated the challenges experienced by staff during these episodes of care. These included lack of confidence about diagnosing and/or treating seizures at the end of life, difficulties finding appropriate advice, and practical aspects of co-ordinating care with other teams or locations. Responses highlighted the

anxieties felt by inexperienced nurses, GPs and paediatricians who were prescribing high doses of midazolam in the absence of adequate guidance for symptom control, particularly when care was provided outside a hospital environment. Many mentioned the emotional toll for staff if seizures proved difficult to control, and when families experienced distress resulting from this.

Discussion

This study reports on 18 children identified over a ten year period in the south west of England. Estimates from the West of England Child Death Overview Panel (CDOP) suggest life-limiting illness in children aged 1-18 leads to 35-40 expected deaths per year in the southwest region, of which epilepsy is a contributing factor in 5% (SUDEP excluded). (Personal communication, V Sleep, CDOP). These figures would suggest that our cohort of cases is likely to represent the majority of cases of death involving epilepsy in this area, and is illustrative of standard practice in the region over that time period.

In an attempt to ensure as peaceful a death as possible, clinicians need to anticipate likely challenges to effective symptom control and have the means to manage potential complications. A pro-active approach, anticipating and planning for the management of seizures if and when they occur, could reduce some of the suffering and anxiety surrounding the management of this scenario. Advanced care planning, involving timely discussion of potential complications and management approaches with families and staff, can ensure that all can be prepared and intervene promptly⁵, and it was reassuring to see evidence of such planning in all cases in this cohort.

The results above demonstrate the range of drugs used and doses prescribed, and variable adherence to available guidelines. Although most clinicians referred to the Rainbows Symptom Control Manual¹⁴, the APPM Formulary¹⁶, or the Children's BNF¹⁸ for advice on doses, specific advice on symptom management for status epilepticus in EOL care was reportedly difficult to find, inconsistent in content, and short on detail. Case notes and email correspondence reveal anxiety amongst front-line staff when using generous doses of midazolam and phenobarbital, and caution

when escalating doses or introducing new medications, but also recognition of the need to provide effective symptom control as quickly and safely as possible for the benefit of the child and family. Many clinicians relied on the “phone-a-friend” method of support in these circumstances, seeking advice from colleagues in neurology or palliative care in regional or national specialist units. Given the lack of consensus and weak evidence base for management of seizures in these circumstances this perhaps reflects a willingness to approach each situation on a case-by-case basis. We suggest that the evidence base for guidance will not improve until the learning from these individual experiences is collated and shared.

It is important to maintain an overview of the total symptom control process whilst at the same time being cautious about the use of drugs which can exacerbate seizures. Eleven of the 19 episodes involved the use of infusions of levomepromazine as antiemetic or sedative. In five of these examples the dose was escalated rapidly as it was delivered in a syringe driver in combination with other medications, such as diamorphine, that were being titrated for pain control. Unfortunately, levomepromazine lowers seizure threshold¹⁹, and it is possible that this rapid dose escalation may have precipitated the onset of seizures in some cases.

Many antiepileptic drugs are not available in appropriate formulations for parenteral use, or require IV infusions, which are not easy to maintain outside a hospital setting¹³. Literature reports the successful use of levetiracetam in subcutaneous infusions in adults requiring palliative care^{20,21}, and this option may be a useful adjunct for consideration in similar cases in the future.

The practical aspects of caring for a child with complex symptom control, frequently a high level of physical or nursing need, in an emotionally heightened situation, meant that many families chose admission to a hospice for end-of-life care. The hospice units in this region have one-to-one nursing provision around the clock, with flexible medical attendance on site, so much of the responsibility for individual patient management sits with the nurse on duty with the child. Prolonged use of infusions (up to 27 days) was logistically challenging for staff supporting children at home or in

hospices, but ensured that the child and family remained in the location of their choice as death approached. Despite the use of high doses of midazolam or phenobarbital, there were no instances where hospital admission was required.

This study is limited by its 10 year retrospective time frame, and a methodology based on reviews of case notes meaning that some relevant detail may have been missed, but we attempted to overcome this by email or discussion with involved staff in many cases.

Conclusions

The current management of seizures in children approaching the end of their lives is complicated, inconsistent, and challenging for families and for staff in our region. A structured approach encompassing a holistic overview of care, proactive management, and consistent pharmacological approaches to seizures with advice on supporting care could result in improved symptom control for the child, and an enhanced experience for families and staff providing end-of-life support. We note the recent publication of draft NICE guidelines on End of Life care for Children and Young People²², and welcome their recommendation for further research in this key aspect of symptom control.

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NH, PS, CM, MB and KT were involved in the design of the project and securing funding. NH, CM, KT and MB sourced data. All authors were involved in data analysis and interpretation, and in drafting this paper.

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