Subcutaneous levetiracetam for the management of seizures at the end of life

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ABSTRACT

Objectives To report the results of a combined case series analysis of subcutaneous levetiracetam (Keppra) for the management of seizures in palliative care patients.

Methods A comprehensive literature review on the use of subcutaneous levetiracetam was performed, and these data were combined with a prospective observational audit of its use in terminal care undertaken in a regional palliative care network.

Results 7 papers were identified from the literature review-four case reports and three observational case series-reporting on a total of 53 cases where subcutaneous levetiracetam was administered. We report 20 further cases of subcutaneous levetiracetam administration from a prospective observational audit. Doses ranged from 250mg to 4000 mg daily. Oral to subcutaneous conversion ratios where stated were 1:1. Levetiracetam was reported as the sole administered antiepileptic drug (AED) in eight cases, and no seizures were reported until death in five cases. Five were switched back to enteral levetiracetam. In seven cases, levetiracetam was combined with AEDs to provide seizure control at the end of life. There was one report of a sterile abscess after 25 days of continuous subcutaneous administration.

Conclusions Combined analysis of 73 reported cases of subcutaneous levetiracetam suggests this treatment may have a role in the management of seizures at the end of life. However, randomised controlled trials are urgently needed to establish the efficacy and tolerability of subcutaneous levetiracetam administration. If proven to be safe and effective, subcutaneous levetiracetam offers the potential to prevent and treat seizures without causing unnecessary sedation at the end of life.

INTRODUCTION

Prevalence of seizures at the end of life

Seizures are common at the end of life and are usually a manifestation of cerebral neoplasms. A systematic review of seizures in the end of life phase of patients with primary or metastatic brain tumours revealed a prevalence of 6%–56% and the studies included were from hospice, hospital and home care settings.[1] Seizures cause distress for both patients and families and risk brain damage if prolonged and uncontrolled.[2] As such, seizures are considered to be a palliative care emergency.[3] There is a range of pharmacotherapy options and routes of administration to manage seizures in palliative care.[1 3 4] Many palliative care patients are initially commenced on an oral antiepileptic drug (AED); however, the oral route becomes less reliable as the disease progresses and end of life approaches. Caregivers of patients with primary brain tumours suggest the prevalence of dysphagia is 40% in the last 3 months of life, and this increases to 70% in the last weeks of life.[5 6] Not much is known about the transition from oral AEDs to other routes when the oral route is lost.

Current management of seizures at the end of life in a palliative setting

In a palliative care setting, it is common practice to stop established oral AEDs once the oral route is lost and switch to an alternative AED via the subcutaneous (SC) route. The therapeutic options via the subcutaneous route are limited. An example from clinical practice might be stopping oral levetiracetam and commencing a syringe driver with a continuous subcutaneous infusion of midazolam. The starting doses of midazolam range from 10 to 30 mg, with the dose escalated if seizures are witnessed and the addition of phenobarbital if seizures remain uncontrolled.[3 4]

While benzodiazepines and barbiturates achieve effective seizure control,

they also induce sedation. This sedative effect may be desirable in agitated patients. However, the sole use of sedating medications risks ongoing sedation of a patient who might otherwise have regained consciousness following a postictal period. Therefore, there is a need to explore a non-sedating alternative should this be felt to be appropriate.

Use of off licence subcutaneous levetiracetam offers the possibility of maintaining seizure control when the oral route is lost without increasing the level of sedation[7].

Mode of action

Levetiracetam works in a novel way by 'modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain'.[8] Unlike carbamazepine, phenytoin and phenobarbital, it is not known to interact with dexamethasone or to induce cytochrome P450.[9] Levetiracetam is increasingly used for this reason in patients with primary or metastatic brain tumours who are likely to require steroid treatment.[10] As the evidence leads to the increasing use of levetiracetam as a monotherapy for seizure prophylaxis in patients with primary or metastatic disease, this may place an added onus on palliative medicine clinicians to continue its use for as long as possible.[11 12]

However, prescribing considerations include that: incremental dose changes should not usually be made more frequently than 2 weekly, dose adjustment is required in renal failure and a tapered reduction is needed before stopping levetiracetam.[13 14] This requirement that levetiracetam is not stopped abruptly may be an important consideration for clinicians.

Licenced routes of administration

Levetiracetam is available as tablets, oral solution or in a solution of 100 mg/mL and is licenced in the UK for intravenous infusion.[14] Intravenous levetiracetam is increasingly used in the treatment of status epilepticus.[11 12]

Subcutaneous administration therefore represents an off licence use of levetiracetam; however, as the oral route is frequently lost in patients with brain tumours towards the end of life, it represents a clinically very important route of administration, where intravenous administration is not practicable.[1 5]

LITERATURE REVIEW

A search of EMBASE, Medline, CINAHL, ClinicalTrials.gov and the WHO International Trials Registry for 'subcutaneous AND levetiracetam' or 'subcutaneous AND keppra' or 'levetiracetam SC' (see online appendix 1) on the 16th of July 2015 and updated the search on the 2nd of August 2016 (see online appendix 2). The search was not restricted to English language papers. Eighty-three records were identified through searches and six records identified from other sources (see figure 1). Seven papers were included in the review following review of the title, abstract and full paper by two authors (AS and JC).[7 15–20] These included four case reports and three case series reports. There were no randomised controlled trials identified as being registered on either of the trials databases. Six of the included papers were in English, and one was in French, which was translated by a Palliative Medicine Consultant (KN) with prior experience in translating French language literature.

Figure 1 PRISMA diagram

METHODS

Abstract screening and data extraction were performed by two authors (AS and JC). No statistical analysis or meta-analysis was performed as this was felt to be inappropriate given the inherently high risk of bias in case reports and case series owing to the study design.

Our primary outcomes were

1. to assess the efficacy of subcutaneous levetiracetam administration (as measured by the number of patients with no reported seizure activity over the total reported periods)
2. to assess the tolerability of subcutaneous levetiracetam (as measured by the number of patients reported to have experienced any adverse event or site reaction).

Our secondary outcome measures were

1. to document the mode of subcutaneous administration (bolus vs syringe driver)
2. to document the diluent used
3. to document the dose used and any conversion rate used if the patient had previously been taking levetiracetam by another route of administration
4. to identify where any seizure activity was reported whether any breakthrough treatment was required for this
5. to document the concomitant use of any other AEDs
6. to document the result of any serum levetiracetam level taken during subcutaneous administration
7. to document the duration of treatment.

Articles were excluded if they contained no novel data relating to the subcutaneous administration of levetiracetam. We did not exclude articles that failed to address our outcome measures.

Results of literature review

Fifty-three adult patients were reported in seven articles to have received subcutaneous levetiracetam.[7 15–20]

Three patients were reported to have been observed to have seizures or myoclonus while on subcutaneous levetiracetam.[17] However, 36 patients concomitantly received other AEDs including midazolam, although the doses of these were not consistently reported.[17 19]

Three patients were observed to have site reactions; however, all of these patients were documented to have had other medications mixed in the syringe driver including midazolam, metamizol, morphine and butylscopolamine. One of these patients developed a rash and as a result treatment was discontinued and the rash resolved.[17]

Two patients received intermittent subcutaneous boluses diluted in 100 mL 0.9% sodium chloride administered every 12 hours over 30 min.[13 14] Five patients received intermittent subcutaneous boluses diluted to 2.5 mg/mL, although the total dose was not reported.[18]

Forty-six patients received levetiracetam by continuous infusion via syringe driver. The doses administered ranged from 250 mg to 4000 mg daily and where the dose was converted from oral administration a conversion ratio of approximately 1:1 was reported. Three patients had serum levetiracetam levels checked, and these were found to be therapeutic while receiving subcutaneous levetiracetam.[15 17 18]

In total, 40 patients continued treatment until death. Four were transferred to hospice and were lost to follow-up.[17] Three patients' clinical status improved, recovering their oral route and were therefore switched back to oral antiepileptics. One was discontinued due to rash.[17] Data on duration of treatment were not available in five patients.[18] The duration of treatment ranged from 1 to 47 days.

PROSPECTIVE AUDIT

Methods

Ethical consideration

We carefully considered the need for ethical approval to document subcutaneous levetiracetam administration within the region. This study was a clinical audit documenting the usual practice of a palliative care clinician at the end of an episode of care. The study did not demand a change in the treatment received by the patient, and therefore NHS ethical approval was not required.[21] Confidentiality was maintained by recording a minimal set of data on each patient, and these data were anonymised prospectively. Wherever possible, physicians explained the rationale and use of this off licence prescription to the patient or the patient's next of kin as they would with any other off licence medication.[22]

Data collection

We developed a data collection sheet as a group based on the outcomes identified in the literature review. We took care to only document data directly relevant to the audit to minimise the risk of recorded data being potentially patient identifiable. Three authors (AS, VB and OB) then independently piloted the form and further amendments were made subsequently (see online appendix 3). Data from the completed collection sheets was collated (AS) on an individual patient basis for each collected outcome.

RESULTS

Data were collected over a 1-year period from July 2015 to July 2016. In total, six centres within the Thames Valley region took part. These included: two NHS hospitals, two NHS hospices and two independent hospices. All cases reported were adults over 18 years of age and patients under the care of specialist palliative care services, and all (but one community patient) were in an inpatient setting. Twenty episodes of care or cases, representing 18 patients, were collected. One patient was documented to have received subcutaneous levetiracetam on three separate occasions.

In 19 of the 20 cases, patients had been receiving levetiracetam via an alternative route before subcutaneous administration was commenced (see table 1). Seven patients were reported to have been observed to have seizures, myoclonus or twitching while on subcutaneous levetiracetam (see table 2). However, 13 patients concomitantly received other AED including midazolam, phenytoin and phenobarbital, although the doses of these were not consistently reported. One patient was observed to have a site reaction requiring discontinuation, while another developed a sterile abscess after 25 days of treatment. There were no reported systemic adverse events. All patients received levetiracetam by continuous subcutaneous infusion via a syringe driver. The doses administered ranged from 500 mg to 3000 mg daily. Where the dose exceeded 2400 mg in 24 hours, the dose was divided by 50% and given as two 12 hourly syringe drivers. Where the dose was converted from oral administration, a conversion ratio of 1:1 was the most frequently recorded ratio (13/20). No patients had a serum levetiracetam level checked. Of the seven cases of reported seizure activity while on subcutaneous levetiracetam, three resolved with escalation of levetiracetam alone, while others required an increase in the levetiracetam dose as well as midazolam or midazolam was introduced without altering the levetiracetam dose. In total, 12 patients continued treatment until death. In three cases, the patient's clinical status improved with recovery of their oral route, and they were therefore switched back to

Table 1 Diagnosis, antiepileptic drugs used, dose and conversion ratio. Case 1 reflects one patient commenced on subcutaneous levetiracetam on three separate occasions, represented as a, b and c

Case	Diagnosis	Other AEDs prescribed pre-SC levetiracetam	Other AEDs prescribed during SC levetiracetam	Diluent	Initial dose (24 hours)	Dose ratio
1a	Secondary brain malignancy	Levetiracetam (750 mg BD PO) Phenytoin (100 mg BD PO)	Phenytoin (100 mg BD PO)	Water	1500 mg	1:1
1b	Secondary brain malignancy	Levetiracetam (750 mg BD PO) Phenytoin (100 mg BD PO)	Phenytoin (100 mg BD PO)	Water	1500 mg	1:1
1c	Secondary brain malignancy	Levetiracetam (750 mg BD PO) Phenytoin (100 mg BD PO)	Nil	Water	1500 mg	1:1
2	Secondary brain malignancy	Levetiracetam (250 mg BD PO)	Nil	Water	2000 mg	1:4
3	Progressive neurological disease	Levetiracetam (250 mg BD PO) Lamotrigine (125 mg BD PO) Phenytoin (230 mg OD PO)	Midazolam (10 mg SC CSCI)	Water	500 mg	1:1
4	Primary brain malignancy	Levetiracetam (1000 mg BD PO) Clobazam (10 mg BD PO)	Nil	Water	2000 mg	1:1
5	Primary brain malignancy	Levetiracetam (500 mg BD IV)	Phenobarbital (400 mg SC CSCI)	Water	1000 mg	1:1
6	Secondary brain malignancy	Levetiracetam (250 mg OD PO)	Nil	Water	500 mg	1:2
7	Epilepsy	Sodium valproate (1250 mg BD PO changed to 600 mg four times a day IV)	Nil	Water	500 mg	n/a
8	Secondary brain malignancy	Levetiracetam (500 mg BD PO) Midazolam (5 mg SC ON)	Midazolam (5 mg SC ON)	Water	1000 mg	1:1
9	Secondary brain malignancy	Levetiracetam (1500 mg BD PO) Sodium valproate (400 mg BD PO) Midazolam (15 mg SC CSCI)	Midazolam (15–40 mg SC CSCI)	Water	2000 mg	1:0.6
10	Secondary brain malignancy	Levetiracetam (500 mg BD PO) Phenytoin (250 mg/300 mg PO)	Midazolam	Water	1000 mg	1:1
11	Secondary brain malignancy	Levetiracetam (500 mg increased to 750 mg BD PO)	Midazolam	Water	1000 mg	1.5:1
12	Primary brain malignancy	Levetiracetam (750 mg BD PO) Lamotrigine (100 mg BD PO)	Nil	Water	1500 mg	1:1
13	Epilepsy	Levetiracetam (1500 mg BD PO) Phenytoin (450 mg OD PO) Clonazepam (1 mg OD PO)	Midazolam (5–15 mg SC CSCI plus 3×2.5 mg doses)	Water	2400 mg	1:0.8
14	Primary brain malignancy	Levetiracetam (1500 mg BD PO) Sodium valproate (200 mg BD PO) Clobazam (10 mg OD PO)	Midazolam (40–60 mg SC CSCI)	Water	2400 mg	1:0.8
15	Epilepsy	Levetiracetam (500 mg BD PO, reduced to 500/250 mg)	Midazolam (15 mg SC CSCI)	Water	750 mg	1:1
16	Primary brain malignancy	Levetiracetam (1500 mg BD PO) Clobazam (10 mg prn) Midazolam (15 mg SC CSCI)	Midazolam (12.5–15 mg SC CSCI)	Saline	1500 mg (12 hourly)	1:1
17	Primary brain malignancy	Levetiracetam (500 mg BD PO, then IV)	Nil	Water	1000 mg	1:1
18	Secondary brain malignancy	Levetiracetam (1000 mg BD PO)	Midazolam (2.5–5 mg SC PRN nine administrations recorded, total dose 32.5 mg)	Water	2000 mg	1:1

AEDs, antiepileptic drugs; BD, twice daily; CSCI, continuous sucbutaneous infusion; OD, once daily; ON, once nocte; PO, per os; PRN, as required; SC, subcutaneous. .

oral antiepileptics. The duration of treatment ranged from 21 hours to 26 days.

DISCUSSION

The data identified represent very low quality data, and as a result, no conclusions can be drawn with any certainty.

The use of subcutaneous levetiracetam might be alluring due to the potential avoidance of sedation associated with subcutaneous midazolam or phenobarbital and the ensuing ethical implications.[7] However, the paucity of published and unpublished randomised controlled trials on its use and limited clinical experience currently limit its use. Additionally, there is, as yet, insufficient evidence to clearly demonstrate that therapeutic levels of levetiracetam are achieved when the subcutaneous route of administration is used.

Table 2 Clinical response observed with subcutaneous levetiracetam. *Case 1 was noted to be commenced on subcutaneous levetiracetam on three separate occasions, represented as a, b and c

Case	Seizure frequency prior to commencing SC levetiracetam	Seizure frequency during SC levetiracetam	Duration of SC levetiracetam	Dose changes made during administration of SC levetiracetam	Reactions at injection site	Reason for cessation of SC levetiracetam	Death on S/C levetiracetam
1a*	1–5 per day	Daily until dose increased then none further	14 days	Increased to 1750 mg	None	Recovered oral route	No
1b*	Once daily	None	16 days	Phased reduction with reintroduction of oral preparation	None	Recovered oral route	No
1c*	Once weekly	None	21 hours	Nil	None	n/a	Yes
2	Once daily	None	9 days	Nil	None	n/a	Yes
3	None recent	None	3 days	Nil	None	n/a	Yes
4	None recent	None	8 days	Nil	None	n/a	Yes
5	Unknown	Ongoing tremor until phenobarbital started, one grand mal seizure	6 days	Increased to 1500 mg for 48 hours, then 2000 mg for 72 hours and then 3000 mg for 6 days	None	n/a	Yes
6	1–2 per month	None	7 days	Nil	None	n/a	Yes
7	Unknown	None	?	Nil	None	n/a	Yes
8	One in 4 months	None	5 days	Nil	None	n/a	Yes
9	Two in preceding months	Two seizures until midazolam increased, then none further	11 days	Nil	None	n/a	Yes
10	Multiple since February 2016	None until last 2 days of life	13 days	Increased to 1500 mg	None	n/a	Yes
12	Unknown	Unlikely, twitching noted but felt to not represent seizure activity	5 days	Nil	None	Rationalised number of syringe pumps in last hours of life	No
13	Nil noted	Nil	26 days	Nil	Sterile abscess after 25 days	Recovered oral route	No
14	Three in 2 months	2–3 seizures a day	3 days	Nil	None	n/a	Yes
16	None recent	None	6 days	Nil	None	n/a	Yes
17	One in 2 months	None	6 days	Nil	None	Increasing agitation, switched to 20–30 mg midazolam	No
18	Partial seizures daily, occasional grand mal seizures	Daily partial seizures	3 days	Nil	Recurrent areas of panniculitis at Subcutaneous needle sites reproducibly appearing after 10–12 hours necessitating movement of the site	Site reaction	No

The results of this clinical audit compare favourably with previously published case series and case reports. Based on this combined data, the administration of levetiracetam via a continuous subcutaneous syringe driver appears to be well tolerated and causes site reactions infrequently. Despite early concerns about its high osmolality,[17] the use of an intermittent subcutaneous bolus has only been reported in the literature in two cases.[15 16] The available data therefore currently appear to support the use of continuous subcutaneous infusion rather than intermittent bolus infusions.

Three out of the four reported site reactions occurred when levetiracetam was mixed with other medications in the syringe driver. It would appear prudent to avoid this practice until compatibility and stability data relating to its degradation and osmolality when administered via the subcutaneous route become available.

Given the uncertainty regarding the pharmacokinetics, absorption and bioavailability of levetiracetam when administered subcutaneously any seizure activity seen during subcutaneous levetiracetam infusion should continue to be managed in the established way with either subcutaneous midazolam or phenobarbital.

Limitations

This observational audit, combined with the findings of the literature review, as discussed earlier, represents very low quality evidence and is a high risk of bias due to the study design. It should also be noted that two of the studies were only available to the authors in abstract form, and additional correspondence with the authors was not entered in to.[18 19] Therefore, we can only comment on the data available to us.

Although palliative care physicians within the region were encouraged to complete a data collection sheet following each episode of care, it is uncertain whether all cases of subcutaneous levetiracetam administration within the region were documented. We therefore cannot exclude selection bias within the data.

In minimising the amount of patient data recorded, it should be noted the age, gender, comorbidities, drug history (other than AEDs) and concomitant current medical diagnoses including hypoglycaemia and sepsis were not documented. The risk of confounding variables and drug interactions relevant to the efficacy of levetiracetam therefore cannot be excluded.

CONCLUSION

Implications for practice

The efficacy and tolerability of off licence subcutaneous levetiracetam administration remain to be established as randomised controlled trials, and a subsequent systematic review has yet to be under taken. If it is to be used to prevent seizures when there is no licenced alternative route available, it is important to use levetiracetam alone in a syringe driver, not to exceed 2000 mg in one 30 mL syringe driver and to monitor for site reaction and seizure activity. In the event of a prolonged seizure or status epilepticus despite subcutaneous levetiracetam, the administration of benzodiazepines (with or without phenobarbital) remains the first-line agent when treating the seizure. Please note that we have developed a guideline regionally for adults (see online appendix 4), and additional guidance has also recently been published.[23]

Implications for research

The combined case report, series and audit data present 73 reported cases of subcutaneous levetiracetam administration. However, it is based on category 4 and 5 evidence. While case reports, series and audit may provide some insight to clinical practice in palliative care, however, the onus is on the specialty to improve the evidence base.[24 25] Randomised controlled trials are urgently needed to establish the efficacy and tolerability of subcutaneous levetiracetam administration. Additionally, studies on the compatibility, stability and bioavailability of levetiracetam when administered via the subcutaneous route are also urgently required.

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Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval This study was a clinical audit documenting the usual practice of palliative medicine physicians and followed the standards outlined by the host organisations. The study did not demand a change in the standard of care or treatment received by patients. Therefore, this study was not considered Research by the NHS, and therefore NHS ethical approval was not required.

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