NHS

Health Education Thames Valley

Management of Seizures at the End of Life

A new way forward?

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- Explore the burden of seizures at the end of life and current practice
- Describe the role of Levetiracetam as an anti-epileptic
- Recognise and review the published data
- Present novel data

PREVIOUSLY ON...

- Seizures occur in approximately 13% of palliative care patients
  - 25% to 50% of palliative patients who develop seizure activity have brain metastases
  - Of patients with primary brain tumours 30-70% suffer seizures

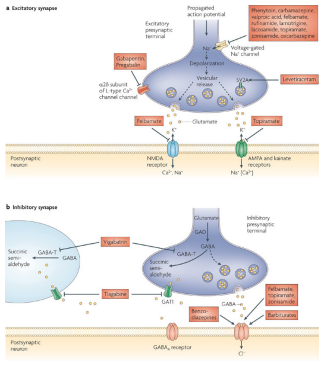
Tradounsky, Golda. "Seizures in palliative care." *Canadian Family Physician* 59.9 (2013): 951-955.
Pruitt, Amy A. "Medical management of patients with brain tumors." CONTINUUM: Lifelong Learning in Neurology 21.2, Neuro-oncology (2015): 314-331.

1a) In patients with pre-existing epilepsy controlled by PO medication that are imminently dying (prognosis <1 week), and are no longer able to take PO tablets, what is generally your first-line course of action? (one_of)

answer	votes	% of vote
Stop all anti-epileptics, prescribe only p.r.n. benzodiazepine (buccal or SC midazolam or PR diazepam)	18	18%
Start parenteral midazolam	68	69%
Start parenteral levetiracetam	4	4%
Start parenteral phenobarbital	3	3%
Start parenteral valproate	1	1%
Other (please supply information in question 1b below)	5	5%

2a) In patients with pre-existing epilepsy controlled by PO medication that are *not* imminently dying (prognosis >1 week), and are no longer able to take PO tablets, what is generally your first-line course of action? (one_of)

answer	votes	% of vote
Stop all anti-epileptics, prescribe only p.r.n. benzodiazepine (buccal or SC midazolam or PR diazepam)	8	8%
Start parenteral midazolam	39	39%
Start parenteral levetiracetam	11	11%
Start parenteral phenobarbital	6	6%
Start parenteral valproate	6	6%
Other (please supply information in question 2b below)	25	25%



Lynch, Berkley A., et al. "The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug Levetiracetam." *Proceedings of the National Academy of Sciences of the United States of America* 101.26 (2004): 9861-9866.

- Searched EMBASE, Medline, CINAHL, ClinicalTrials.gov and the WHO International Trials Registry for
  - "subcutaneous AND Levetiracetam" or "subcutaneous AND keppra" or "Levetiracetam SC"
- 83 records were identified through searches and 6 records identified from other sources
- 7 papers were included in the initial review following review of the title, abstract and full paper by two investigators
- 2 further have been added subsequently
- 5 case reports and 4 case series

Literature Review Outcomes

- 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 versus 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 anti-epileptics
6. To document the result of any serum Levetiracetam level taken during subcutaneous administration
7. To document the duration of treatment

- 86 patients with a range of diagnoses were reported to have received subcutaneous Levetiracetam

Efficacy:

- 5 patients reported to have had seizures or myoclonus whilst on subcutaneous Levetiracetam

Tolerability:

- 3 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 metamizol, morphine, and butylscopolamine
- One of these patients developed a rash and as a result treatment was discontinued and the rash resolved

Dose:

- Oral to subcutaneous conversion ratio of 1:1 or 1.3:1 was reported

Delivery mechanism:

- 78 patients received Levetiracetam by continuous infusion via syringe driver with doses administered ranging from 250mg-4000mg daily
- 7 patients received intermittent subcutaneous boluses

Concomitant therapy:

- 57 patients received additional AEDs, with at least 29 of these receiving midazolam

Duration of use:

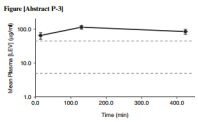
- Duration of treatment ranged from 1 to 47 days stopping largely due to death but 4 patients were transferred from the treating unit, 3 recovered their oral route, and one was stopped due to side effects (rash)

Monitoring:

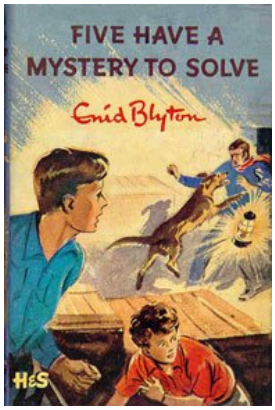
- 3 patients had serum Levetiracetam levels checked and were therapeutic whilst receiving subcutaneous Levetiracetam.

Animal Studies:

- Evidence that subcutaneous administration is:
  - Tolerated
  - Plasma levels are at therapeutic levels within 15minutes
  - And remain so for 7 hours



Hardy, B. T., E. E. Patterson, and J. M. Cloyd. "Subcutaneous Administration Of Levetiracetam In Healthy Dogs." *Journal of Veterinary Internal Medicine* 25.3 (2011): 741.



Methods:

- Following the completion of an episode of care data was recorded on anonymised data collection sheets
- A minimum data set was agreed based on the outcomes identified in the literature review
- All hospices and specialist palliative care teams within the region were invited to submit data and the following offered data:
  - 2 NHS hospitals
  - 2 NHS hospices
  - 2 independent hospices
- Data was collected from July 2015- July 2016

20 episodes of patient care (18 patients)
19 of the episodes where patients had been established on Levetiracetam prior to loss of oral route

Efficacy:

- 7 patients were reported to have been observed to have seizures or myoclonus whilst on subcutaneous Levetiracetam
- 2 resolved with escalation of Levetiracetam alone or in concert with midazolam

Tolerability:

- 1 patients was observed to have a site reaction requiring discontinuation
- 1 patient experienced a sterile abscess after 25 days of treatment
- No reported systemic adverse events

Dose:

- A range of oral to subcutaneous conversion ratios were reported with 1:1 being the most common (13/20)

Delivery mechanism:

- All patients received continuous subcutaneous infusion
- Doses ranged from 500mg-3000mg daily
- Where the dose exceeded 2400mg in 24 hours the dose was divided by 50% and given as two 12 hourly syringe drivers
- 19/20 used water as a diluent

Concomitant therapy:

- 9 patients received midazolam
- 1 patient received midazolam and phenobarbital

Monitoring:
- No patients had serum Levetiracetam levels checked

Duration of use:
- Duration of treatment ranged from 21 hours to 26 days
- 12 patients continued treatment until death
- 3 occasions where patients' clinical status improved, recovering their oral route and were therefore switched back to oral anti-epileptics.

Conclusions:
- The data identified represents very low quality data
- Some positive suggestion of efficacy in seizure control
- Administration of Levetiracetam via a continuous syringe driver
- Remains uncertain if therapeutic levels of Levetiracetam are achieved via the subcutaneous route

Review

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

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjspcare-2016-001261).

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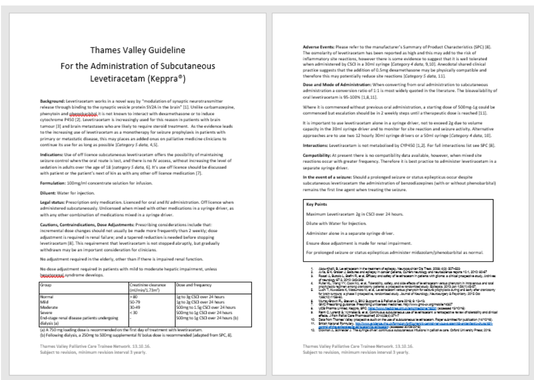
ABSTRACT
Objectives To report the results of a combined case series analysis of subcutaneous levetiracetam (Keppra) for the management of seizures in palliative care patients.
Methods A comprehensive literature review on the use of subcutaneous levetiracetam was performed, and these data were combined 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

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



Thames Valley Guideline

For the Administration of Subcutaneous Levetiracetam (Keppra®)

Background: Levetiracetam works in a novel way by "modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain" [1]. Unlike carbamazepine, phenytoin and phenobarbitol it is not known to interact with dexamethasone or to induce cytochrome P450 [2]. Levetiracetam is increasingly used for this reason in patients with brain tumour [3] and brain metastases who are likely to require steroid treatment. 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 places an added onus on palliative medicine clinicians to continue its use for as long as possible [*Category 5 data*, 4,5].

Indications: Use of off licence subcutaneous levetiracetam offers the possibility of maintaining seizure control when the oral route is lost, and there is no IV access, without increasing the level of sedation in adults over the age of 18 [*category 5 data*, 6]. It's use off licence should be discussed with patient or the patient's next of kin as with any other off licence medication [7].

Formulation: 100mg/ml concentrate solution for infusion.

Diluent: Water for injection.

- Maximum Levetiracetam 2g in CSCI over 24 hours.
- Dilute with Water for Injection and administer alone in a separate syringe driver.
- Ensure dose adjustment is made for renal impairment.
- For prolonged seizure or status epilepticus administer midazolam/phenobarbital as normal
- Importance of discussion with patient or next of kin as off-licence

Group	Creatinine clearance (ml/min/1.73m²)	Dose and frequency
Normal	> 80	1g to 3g CSCI over 24 hours
Mild	50-79	1g to 2g CSCI over 24 hours
Moderate	30-49	500mg to 1.5g CSCI over 24 hours
Severe	< 30	500mg to 1g CSCI over 24 hours
End-stage renal disease patients undergoing dialysis (a)	-	500mg to 1g CSCI over 24 hours (b)

Other ongoing work…

Take home messages

- Use of subcutaneous Levetiracetam offers the possibility of maintaining seizure control when the oral route is lost, and there is no IV access, without increasing the level of sedation
- More data needed!
- Role in those not yet on Levetiracetam?

Any questions?