Use of Subcutaneous Levetiracetam at the end of life:
a literature review and audit

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Present the data on use of subcutaneous Levetiracetam for seizure control at the end of life and propose a way forward for practice

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

• 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 authors
• 2 further have been added subsequently
• 5 case reports and 4 case series
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

**Monitoring:**
- 3 patients had serum levetiracetam levels checked and were therapeutic whilst receiving subcutaneous levetiracetam.

**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)
Animal Studies:
• Evidence that subcutaneous administration is:
  — Tolerated
  — Plasma levels are at therapeutic levels within 15 minutes
  — And remain so for 7 hours


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 who had been established on levetiracetam via an alternative 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 patient 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
Implications for practice

- Further evidence is needed to clearly demonstrate efficacy, tolerability and compatibility in syringe driver combinations
- Importance of monitoring for site reactions
- Administration of benzodiazepines in case of ongoing seizure activity remains first line

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73m²)</th>
<th>Dose and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;80</td>
<td>1g to 3g CSCI over 24 hours</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>1g to 2g CSCI over 24 hours</td>
</tr>
<tr>
<td>Moderate Renal</td>
<td>30-49</td>
<td>500mg to 1.5g CSCI over 24 hours</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;30</td>
<td>500mg to 1g CSCI over 24 hours (b)</td>
</tr>
<tr>
<td>End-stage renal disease patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undergoing dialysis (a)</td>
<td></td>
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</tbody>
</table>
Take home messages

• 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
• RCT urgently required to establish efficacy and tolerability
• More data needed on compatibility and diluent

Any questions?