Injectable levetiracetam use in the dog

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Internal Medicine Resident
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Outline

• What is it?
• How does it work?
• What’s good (and bad) about it?
• What can we use it for?
• Does it work?
What is it?

- (S)-α-ethyl-2-oxo-pyrrolidine acetamide
- Keppra®
- Approved in the US in 1999 for adjunctive treatment of partial-onset seizures in adults
- Intravenous formulation approved in 2006 for “bridge therapy”
• Binding site: synaptic vesicle protein 2A (SV2A)
• Modulates the release of neurotransmitters, inhibiting abnormal nerve conduction
• Indirect effects on GABAergic neurotransmission
• Inhibits Na dependent Cl⁻/HCO₃⁻ exchanger
• Affecting K⁺ and high-voltage Ca²⁺ channels

How does it work?
What’s good (and bad) about it?

- Rapidly and almost completely absorbed when given PO, IM
- Minimal CYP450 metabolism
- Minimal protein binding (<10%)
- Minimal drug-drug interactions
- Minimal side effects
- Wide safety margin (minimal side effects at 1200mg/kg)
- Water soluble → IV formulation
- Half-life in people is 6-8h; in dogs 3-4 hours (PO, IM, IV)
- Short time to reach steady-state
What’s bad about it?

• Short half-life → tid dosing
• Expensive
  – Keppra® 1000mg tablets $10/day
    • Canadadrugs.com
  – Generic LEV $2/day
    • Costco
  – Injectable Keppra® $45/500mg vial
    • UVIS price
What do we use it for?

**Oral LEV**
- 2\textsuperscript{nd} or 3\textsuperscript{rd} line therapy for dogs and cats poorly controlled on other AEDs

**Injectable LEV**
- IV therapy for status epilepticus and cluster seizures
- SQ injection for at-home therapy
Where’s the evidence?

- Patterson et al 2008
  - ~20mg/kg LEV IV, IM and PO safe and well tolerated
  - $t_{1/2} = 180$ min
  - No necrosis when given IM or intentionally extravasated
  - 100% bioavailability (IM, PO, extravasated)

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Intramuscular, intravenous and oral levetiracetam in dogs: safety and pharmacokinetics

E. E. Patterson*, V. Goel†, J. C. Cloyd‡, T. D. O’Brien‡, J. E. Fisher†, A. W. Dunn* & I. E. Leppik†,§,‖


Intravenous (IV) levetiracetam (LEV) is available for humans for bridge therapy when the oral route is unavailable. We investigated the safety and pharmacokinetics of LEV administered intramuscularly (IM), IV, and orally to dogs. Six Hound dogs received 19.5–22.6 mg/kg of LEV IM, IV and orally with a wash-out period in between. All dogs received 500 mg LEV orally and 5 mg
Where’s the evidence?

• Dewey et al 2008
  – 60mg/kg IV bolus safe and well tolerated
  – $t_{1/2} = 4h$
  – Plasma [LEV] within or above therapeutic range for >8h

Original Study

Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs

Curtis W. Dewey, DVM, MS, DACVIM (Neurology), DACVS, Kerry S. Bailey, DVM, Dawn M. Boothe, DVM, MS, PhD, DACVIM, DACVCP, Britton L. Badgley, LVT and Crisanta Cruz-Espindola, BS

Where’s the evidence?
Where’s the evidence?

• Volk et al 2008
  – Prospective, open-label study of 14 dogs
  – 8/14 responded (10mg/kg); 1 more responded at 20mg/kg
  – 6/9 responders had increased seizure frequency after 4-8 months
Where's the evidence?

• Platt et al 2007
  – Case report
  – 6m CKCS pharmacoresistant to PB, KBr and gabapentin
  – Responded to LEV

Refractory Seizures Associated With an Organic Aciduria in a Dog

A 6-month-old, female Cavalier King Charles spaniel exhibited seizures that were difficult to control with standard anticonvulsants over a 12-month period. The diagnosis of an organic aciduria with excessive excretion of hexanoylglycine was determined when the dog was 20 months old. Recurrent and cluster seizures were eventually controlled with the addition of levetiracetam to potassium bromide and phenobarbital. J Am Anim Hosp Assoc 2007;43:163-167.
Where’s the evidence?

• Prospective, double-masked, randomized, placebo-controlled study for the treatment of status epilepticus and cluster seizures with IV levetiracetam in dogs
  
• Inclusion criteria
  – Single seizure lasting >5 minutes, or >1 seizure without regaining consciousness in between
  – 3 or more seizures in a 12 hour period within 24h prior to admission
  – Seizure while in hospital
  
• Exclusion Criteria
  – Hypoglycemia, hypocalcemia or uremia
Study Design

- **SE/ARS**
- **Present to ER**
- **In-hospital seizure or ongoing SE**
- **Standard of care**
- **Tx diazepam and LEV/placebo**
- **Discharged after 24h w/o seizures**

Discharged after 24h w/o seizures
Study Design

• 19 dogs included
• LEV/placebo bolus over 5 min
  – 30mg/kg (n=5) or 60mg/kg (n=4); 0.9% NaCl (n=10)
• Primary endpoints
  – % responders (no further seizures after experimental intervention)
  – # of seizures until 24h seizure free
  – # of hours until 24h seizure free
  – % all-cause mortality while in hospital
  – # in hospital episodes of SE
  – Vomiting, diarrhea, ataxia, or decreased alertness
• Plasma [LEV] measured at 15, 45 and 180min
## Patient Baseline Info

<table>
<thead>
<tr>
<th></th>
<th>LEV group</th>
<th>Placebo group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>3.0 (1.5 - 12.0)</td>
<td>5.05 (0.2 - 11.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>30.0 (5.2 - 43.0)</td>
<td>11.7 (3.4 - 42.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Seizure onset (mos)</td>
<td>10 (0 - 54)</td>
<td>3.5 (0 - 90)</td>
<td>0.84</td>
</tr>
<tr>
<td># seizures in 12h before presentation</td>
<td>3 (2 - 9)</td>
<td>5 (1-15)</td>
<td>0.34</td>
</tr>
<tr>
<td>Previous AED Tx</td>
<td>4/9</td>
<td>5/10</td>
<td>0.66</td>
</tr>
<tr>
<td>Idiopathic epilepsy</td>
<td>6</td>
<td>4</td>
<td>n/a</td>
</tr>
<tr>
<td>Inf CNS Dz</td>
<td>1</td>
<td>3*</td>
<td>n/a</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>0</td>
<td>2*</td>
<td>n/a</td>
</tr>
<tr>
<td>Metabolic Dz</td>
<td>1</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1</td>
<td>1</td>
<td>n/a</td>
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</tbody>
</table>
# Primary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>LEV group</th>
<th>Placebo group</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Responder</td>
<td>5/9</td>
<td>1/10</td>
<td>0.057</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>2/9</td>
<td>4/10</td>
<td>0.63</td>
</tr>
<tr>
<td># seizure until 24h seizure free</td>
<td>0 (0-8)</td>
<td>1.5 (0-2)</td>
<td>0.25</td>
</tr>
<tr>
<td># hrs until 24h seizure free</td>
<td>24 (24-48)</td>
<td>30.5 (24-36)</td>
<td>0.23</td>
</tr>
<tr>
<td># episodes of SE</td>
<td>0 (0-2)</td>
<td>0 (0-0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Ataxia</td>
<td>3/9</td>
<td>1/10</td>
<td>0.30</td>
</tr>
<tr>
<td>Alertness</td>
<td>4/9</td>
<td>3/10</td>
<td>0.65</td>
</tr>
<tr>
<td>Vomiting/Diarrhea</td>
<td>1/9</td>
<td>1/10</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Plasma [LEV]

Mean plasma [LEV] (µg/ml; logarithmic scale)

Time (min)

- 60mg/kg
- 30mg/kg
Conclusions

• IV LEV appeared safe and well tolerated in clinical patients
• Trend toward better response
• Different etiology may have been responsible
Study #2 SQ Levetiracetam

- 4 purpose-bred hounds
- Single SQ injection of 60mg/kg
- Plasma [LEV] measured at 15, 120 and 420min
- Monitored for sedation, ataxia, vomiting, diarrhea, and pain at injection site
<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Plasma [LEV] (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>65.2 ± 29.5</td>
</tr>
<tr>
<td>120</td>
<td>114.5 ± 10.5</td>
</tr>
<tr>
<td>420</td>
<td>84.9 ± 20.6</td>
</tr>
</tbody>
</table>
Adverse effects

- No CNS signs
- No GI signs
- No discomfort on palpation of injection site
Conclusions

• Rapidly achieves therapeutic concentration
• Remains above therapeutic range for >7h
• Well tolerated
• Consider for at home use in conjunction with or as alternative to rectal diazepam
Acknowledgements

• Dr. Ned Patterson
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  – Alistair McVey DVM, Alisa Craig PharmD, Aaron Dunn DVM, Robert Hardy DVM, Beth Olmstead CVT
• School of Pharmacy Epilepsy Research and Education Program
  – Ilo Leppik MD, James Cloyd PharmD, John Rarick BS
• ER Staff and Interns
• Kathy Stuebner and The CIC
• Resident mates
Questions?

The Bobcats

Morning Bob.
Oh hey Bob.

theoatmeal.com