

Barnes Heller H, Granick M, Van Hesteren M, Boothe DM. Serum levetiracetam concentrations and adverse events after multiple dose extended release levetiracetam administration to healthy cats. J Vet Intern Med. 2018;00:1–4. <https://doi.org/10.1111/jvim.15129>

Objective: To evaluate serum levetiracetam concentration and adverse effects after 11 days of once daily extended release levetiracetam (XRL) administration to healthy cats.

Study Population: 9 healthy privately owned cats.

Methods: XRL 500 mg/cat administered PO q24hrs for 10 days. On day 11 blood was collected at trough, 4, 6 and 8 hours after tablet administration. Owners maintained records of adverse effects. These time were chosen based on the previously determined mean (SD) Tmax of 4.9 (1.6) hours after a single dose XRL administration in healthy cats.

Results:

Median dose 94.3 mg/kg q24 hours

Serum levetiracetam concentrations (ug/mL) >

Median range trough: 7.0 (2.3-14.1)

Median range 4: 82.6 (7.8-125.3)

Median range 6: 92.3 (13.3-97.3)

Median range 8: 72 (22.8 – 96.4)

Minimum therapeutic range in humans (5 ug/mL)

Peak not observed in 4 cats due to missed samples (n =2) and failure to reach maximal concentration by 8 hours (n=2).

Median time of maximal concentration (Tmax) for the remaining 5 cats 5.2 (range 4-6) hours.

Adverse effects minimal and included ataxia (n=1, 1 day), sedation (n=1, 2 days), vomiting/regurgitation (n=1, days 3 and 7 only)

All resolved without dose adjustment or additional treatment.

Why?

- Epileptic seizure are the most common reason cats are presented to neurologists
- The need for 3 times daily long term dosing may lead to poor compliance
- Only 500 and 750 mg XRL tablet sizes are commercially available
- After single dose pharmacokinetic analysis in healthy cats, the recommended dosing interval for 500 mg XRL was once daily

How?

- Prospective trial
- 9 healthy cats owned by University of Wisconsin School of Veterinary Medicine or Veterinary Care Hospital staff or students
- 500 mg XRL tablet PO with food q24hrs at home by owners for 10 days
- Owners kept a log of administration and adverse events

- Hospitalized on day 11 for blood collection and neurologic exam
- Owners administered one 500 mg XRL tablet on day 13 and 15 as weaning to minimize risk of withdrawal epileptic seizures
- Keppra was detected and quantitated in feline serum using a FDA immunoassay approved for humans on a general chemistry analyzer, validated in feline serum.
- No therapeutic reference interval established for cats so used human (5-45 ug/mL).
- Poor cat cooperation results in unattained serum keppra concentrations at 4 (cat 6), 6 and 8 (cat seven) hours. Data reported at those timepoints is from 8 cats.

Problems

- Not a multiple dose toxicity study so may underestimate adverse events
- All cats were greater than or equal to 5 kg so extrapolation to cats weighing less than 5 kg is discouraged.
- Clinical effect of XLR remains unknown

Pereira GQ, Gomes LA, Santos IS, Alfieri AF, Weese JS, Costa MC. Fecal microbiota transplantation in puppies with canine parvovirus infection. J Vet Intern Med. 2018;32:707–711. <https://doi.org/10.1111/jvim.15072>

Why?

- Modification of intestinal bacterial microbiota has been promising in humans and veterinary medicine as adjunctive treatment to enteric disease
- Parvovirus infection can have prolonged recovery and high mortality rate
- Objective to investigate safety and efficacy of fecal microbiota transplantation (FMT) on the clinical recovery of puppies with AHDS

How?

- 66 puppies with parvo at 2 vet hospitals
 - o all dogs < 1 year of age suffering from AHDS admitted to 2 veterinary hospitals in Brazil
- randomized clinical trial
- PCR indicated all animals carried canine parvovirus CPV-2b
- 2 groups
 - o treatment including antibiotics started in all patients at time of admission between 6 and 12 hours before FMT
 - o standard treatment with IV fluids, antibiotics, antiemetics, gastroprotectants,
 - o standard treatment + FMT
 - 10 g of feces from a healthy dog diluted in 10 mL of saline rectally 6-12 hours post admission
 - o safety of FMT was determined by presence or absence of discomfort during and after the procedure and by monitoring vital parameters
- Feces evaluated daily until time of discharge and classified as liquid (diarrhea), pasty, normal or absent.

- Feces for FMT from healthy 6 year old American Pit Bull Terrier (donor) resident at University's kennel fed exclusively a commercial cooked diet, current on vaccinations and deworming, no antimicrobials, vomiting or diarrhea in 6 months. Normal bloodwork, negative for parvo, distemper and Erlichia based on PCR.
 - o 10 g of donor feces diluted in 10 mL of 0.9% NaCl aspirated into 20 mL syringe, connected to urethral catheter, introduced anally and deposited in proximal rectum without sedation or anesthesia.
 - o Patient maintained in lateral recumbency for 2 minutes with pelvis raised to about 45 degrees from surface to aid in diffusion of transplanted contents by gravity.
 - o Performed between 6-12 hours post admission and repeated q48hours until resolution of diarrhea or a total of 5 applications.

Results:

- FMT associated with faster resolution of diarrhea (P < 0.001) and shorter hospitalization time (P=0.001)
 - o Median 3 days in STD + FMT
 - o Median 6 days in STD
- Mortality not significantly different (P=0.174)
 - o 36.4% (12/33) STD
 - o 21.2% (7/33) FMT
- use of 4th or 5th application of FMT was not required, mean number procedures per dog 1.82 (SD 0.68 range 1-3)
- among survivors resolution of diarrhea within 48 hours occurred in:
 - o 4.8% (1/21) STD
 - o 61.5% (16/26) STD + FMT
- dogs with FMT spent fewer days in hosp (P<0.001)
 - o FMT median 3 (1-6), mean 3.31 SD 1.49
 - o STD median 6 (2-15), mean 5.57 SD 2.76
- Problems
 - o No blinding, no placebo
 - o STD + FMT 1.5 mos older on average than STD

Diniz MS, Teixeira-Neto, FJ, Celeita-Rodriguez N, Giroto CH, Fonseca MW, Oliveira-Garcia AC, Lopez-Castaneda B. Effects of 6% Tetrastarch and Lactated Ringer's Solution on Extravascular Lung Water and Markers of Acute Renal Injury in Hemorrhaged, Isoflurane-Anesthetized Healthy Dogs. J Vet Intern Med. 2018;32:712-721.

Why?

- Tetrastarch can cause AKI in humans with sepsis, but is less likely to result in tissue edema than LRS

- Study aims to compare effects of LRS and 6% tetrastarch (TS) (aka 3rd generation iso-oncotic HES) solution volume replacement on EVLW and AKI markers in hemorrhaged dogs
 - o Inhibition of coagulation minimized with 6% TS
 - o Linked to increased risk of death and AKI in people due to renal tubular damage in septic and nonseptic critically ill patients
- Recently published human meta-analysis concluded that generalized restriction to use of TS (EXCEPT in patients with sepsis) are not supported by evidence
- Veterinary patients: insufficient data?
 - o Hyper-oncotic 10% HES solution increased risk of AKI and death in critically ill dogs, but different elimination kinetics prevent extrapolation to 6% TS
- Benefits of TS
 - o Decrease risk of tissue/lung edema by supporting colloid oncotic pressure (COP)
 - o More prolonged increases in CO when used during normovolemic hemodilution or as VR after hypotensive hemorrhagic shock
- EVLW index (EVLWI) is the amount of fluid in the interstitial space and alveolar lumen
 - o In lung edema associated with intravenous volume loading, increased EVLWI is associated with oxygenation impairment (decreased PF ratio)

How?

- 60 healthy English Pointers
- prospective, non blinded, partially randomized cross over study
 - o animals first underwent anesthesia without hemorrhage (controls)
 - o 2 weeks later dogs hemorrhaged under anesthesia
 - o 8 weeks after first hemorrhage underwent another hemorrhage under anesthesia
 - o during the last two anesthetic episodes they were randomly assigned to LRS or TS
 - o volume of shed blood (mL) = $80 \times \text{body weight (kg)} \times [(\text{Hct target} - \text{Hct baseline}) / (\text{Hct average})]$
 - 80 is the estimated total blood volume (mL/kg)
 - target Hct = 33%
 - blood withdrawn over a 30 minute period from 20 gauge catheter in dorsal pedal artery
- randomly received volume replacements with LRS at 3:1 shed blood or TS at 1:1 shed blood
 - o immediately after calculated amount of blood withdrawn
 - o VR with 3 mL LRS or 1 mL TS for each 1 mL blood shed over 30 minutes
 - Volume expansion efficiency (ratio of expanded plasma volume/amount of unfused fluid) of LRS and TS would approach 33% and 100%, respectively.
- anesthesia maintained until 4 hours after VR for EVLW measurements derived from transpulmonary thermodilution cardiac output
 - o central venous catheter to monitor CVP

- 5 mL boluses of ice cold physiologic saline injected over 2-3 seconds into the central venous catheter, temperature monitored by inline thermistor
 - hemodynamic variables were indexed to BSA
 - femoral artery thermodilution catheter to monitor CO
 - CRI LRS 2 mL/kg/hr administered during anesthesia by means of a peristaltic pump
 - Cardiopulmonary data, HCT, TPP recorded at BL, after blood withdrawal, after VR, 0.5, 1, 2, 3 and 4 hours after VR.
- neutrophil gelatinase-associated lipocalin (NGAL) and creatinine concentrations in plasma and urine were measured until 72 hours after VR
 - measured at BL, 4 hours, 24 hours, 72 hours.

Results:

- total volumes during 30 minutes post hemorrhage
 - LRS 75 +/- 14 mL/kg
 - TS 23 +/- 4 mL/kg (P < 0.001)
- Immediately after VR and from 0.5 to 4 hours after VR, TPP was higher in the TS treatment in comparison with the LRS treatment (P < 0.001)
- CI was higher in LRS than TS treatment immediately after VR and at 0.5, 3 and 4 hours.
- SVRI was decreased in the LRS compared to TS immediately after VR and at 3 and 4 hours
- MAP lower immediately after VR in the LRS group compared to TS however MAP was in the target range in all but 3 animals (both groups represented)
- CVP lower in TS treatment than LRS immediately after VR and 2 hours after VR.
- EVLW index (mL/kg) was lower at:
 - 1 hour after TS (10.0 +/- 1.9) compared to controls (11.9 +/- 3.4) (p=0.04)
 - 4 hours after TS (9.7 +/- 1.9), LRS (11.8 +/- 2.7) (p=0.03)
- PaO₂:FiO₂ did not differ between treatments from 0.5 to 4 hours after VR
- Neither fluid produced evidence of lung edema (impaired oxygenation)
- Urine NGAL/creatinine ratio did not differ among treatments and remained below threshold for AKI (120,000 pg/mg)
- LRS administration caused signs of peripheral edema in 3/6 dogs and resulted in increased EVLWI when compared to TS at 4 hours post VR

Points:

- Healthy nonseptic dogs might not compare well to septic patients
- Clinical relevance if oxygenation not impaired?
- COP not measured, decreased COP could have caused peripheral edema
- COP is maintained by 6% HES in spite of decreased TPP caused by dilutional effect
- Rapid rate of LRS administration (150 mL/kg/h)
- Small number of animals to detect differences (underpowered)
- Cannot extrapolate to critically ill patients
- One time administration cannot be extrapolated to ongoing administration

Kwiatkowska M, Tipold A, Huenerfauth E, Pomianowski A. Clinical Risk Factors for Early Seizure Recurrence in Dogs Hospitalized for Seizure Evaluation. J Vet Intern Med. 2018;32:757-763.

Why?

- Early seizure recurrence rate in human hospitals 30-65%
- Determine timing, frequency and risk factors for early seizure recurrence (ESR) among dogs admitted to the hospital for seizure evaluation
- Which patients should be in the ICU

How?

- 922 dogs referred for seizure investigation, 214 patients included
- retrospective study
- included if hospitalized for at least 48 hours and if database was complete and contained information on timing and description of last seizure episode, neurological examination sheet and hospitalization sheet in which seizure occurrence was noted and diagnostic evaluation consistent with tier 2 confidence level (normal MRI and normal CSF)
 - o IE is a diagnosis of exclusion based on the following confidence levels:
 - Tier one: normal interictal neurological examination and normal blood test results
 - Tier two: normal MRI and CSF
 - Tier three: normal electroencephalography results
- findings compared among dogs diagnosed with idiopathic epilepsy (IE), structural epilepsy (StE) and reactive seizures (RS) as well as in all selected cases together

Results:

- 50% of dogs had a seizure while hospitalized
- Average time to ESR was 7 hours
 - o 90% of cases has seizure recurrence in first 12 hours after hospital admission
 - o in the remaining 10% of cases the seizure occurred 12-48 hours after admission
 - o seizure occurred earliest in the reactive seizure group (avg 3.8 hours)
 - StE 6.3 hours
 - IE 10.9 hours
- IE
 - o 53.1% ESR
 - o Abnormal post ictal exam with prosencephalic signs predicted ESR
- StE
 - o 52.2%
 - o abnormal neuro exam (regardless of neurolocalization or symmetry)
 - o Single generalized or focal seizure 72 hours before hospital admission and abnormal neurologic exam predicted ESR

- Most common causes were intracranial neoplasia (62%), vascular inflammatory immune mediated brain disease (35%)
- RS
 - 40.44%
 - Long term antiepileptic monotherapy
 - Most commonly associated with ESR: hypoglycemia, electrolyte imbalances including calcium disorders, intoxications and HE
 - May be due to fact treated symptomatically for seizure without treating or diagnosing underlying cause
- All together ESR predicted by:
 - Abnormal neurological exam
 - Symmetric or asymmetric
 - Multifocal
 - Prosencephalon
 - Cluster seizures
 - Status epilepticus
 - Combo of any of above 72 hours before presentation
- Most common breeds and % that seized in hospital
 - Mixes; 51.9%
 - Border collies 76.9%
 - Labs 33.3%
 - JRTs 75%
 - French Bulldogs 55.5%
- Of dogs that seized in hospital
 - 24.3% had single focal or generalized seizure 72 hours before presentation
 - 71% had cluster seizures, SE or both before admission
- recommendation is to place all dogs in ICU when
 - IE
 - Hospitalize in ICU for 1st 24 hours
 - StE
 - abnormal neurologic exam with any deficits observed
 - single generalized or focal seizure within 72 hours before admission
- Discussion
 - Hospitalization can increase risk of seizure recurrence
 - Increase in blood catecholamine and cortisol concentrations
 - Panting > hypocapnia > increased excitability of neurons that lowers seizure threshold, decreases brain oxygen concentration and increases cellular acidity, decreases glucose availability by worsening BG regulation, decreases ability to resist stress due to weakened immune system
 - Dogs that had seizure prior to hospitalization and had cardiogenic pulmonary edema could have similar mechanisms
- Limitations
 - Less RS than others, presumably due to the euthanasia for poor prognosis
 - Bias due to exclusion of incomplete data sets

- Patients in day ward could have had undiagnosed seizures
- Timeline (2000-2017) due to changes in treatment like IV Keppra
- Owners don't witness all seizures

Barnard L, Barnes Heller H, Boothe DM. Pharmacokinetics of Single Oral Dose Extended Release Letetiracetam in Healthy Cats. J Vet Intern Med. 2018;32:348-351.

Why?

- Poor compliance with repeated PO dosing of anti-epileptics in cats
- Cutting, crushing or breaking the tablets compromises the extended release properties
- Want to prove that serum levetiracetam concentration will remain above 5 ug/mL for at least 24 hours after administration of single dose XRL PO AND will be well tolerated

How?

- 7 healthy cats
- 500 mg/cat PO
- blood collection and neurological exams recorded over 30 hours
- serum levetiracetam quantitated by immunoassay validated in cats

Results

- median dosage 86.2 mg/kg (range 80-94.3)
- mean maximum concentration (C_{max}) of 89.8 +/- 25.8 ug/mL at ~ 5 hours
- serum levetiracetam > 5 ug/mL in all cats by 90 minutes
- mean concentrations 43.7 +/- 18.4 and 4.9 +/- 3.4 ug/mL at 12 and 24 hours respectively

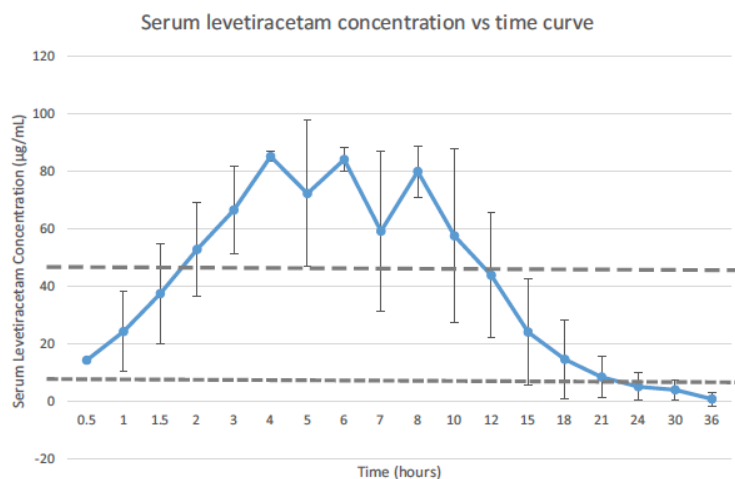


Fig 1. Mean (\pm SD) serum concentration of levetiracetam (μ g/mL) versus time (hours) for 7 cats after a single 500 mg extended-release levetiracetam tablet. Reference range in humans is delineated by dashed lines.

- “A single 500 mg PO dose of XRL safely maintained serum levetiracetam concentrations greater than or equal to 5 ug/mL in healthy cats for at least 21 hours.”
- T1/2 4.1+/-1
- Well tolerated
- Based on the T1/2 an approximately 75% fluctuation would be expected with a 12-hour dosing interval and approximately 93% fluctuation with a 24 hours dosing interval.
- Adverse events: no obvious “serious” adverse events
 - Diarrhea, mild sedation
 - No difficulty with tablet administration noted
- A significantly longer Tmax was identified when XRL was administered with food, compared to dogs receiving XRL after fasting – proposed to be due to slowed absorption rather than delayed elimination

Jaffey JA, Graham A, Van Eerde E, Hostnik E, Alvarez W, Arango J, Jacobs C, DeClue AE. Gallbladder Mucocele: Variables Associated with Outcome and the Utility of Ultrasonography to Identify Gallbladder Rupture in 219 Dogs (2007-2016). J Vet Intern Med. 2018;32:195-200.