Incidence of Postoperative Seizures with and without Levetiracetam Pretreatment in Dogs Undergoing Portosystemic Shunt Attenuation

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**Background:** In dogs with congenital portosystemic shunts (CPS), postligation seizures can be challenging to treat and often result in mortality. Levetiracetam (LEV) is a novel antiepileptic drug that is commonly used in humans with seizure disorders who have hepatic comorbidity.

**Objectives:** To compare the incidence of postoperative seizures in dogs that underwent surgical attenuation of an extrahepatic CPS and preoperatively received either LEV or no anticonvulsant medication.

**Animals:** A total of 126 dogs undergoing attenuation of an extrahepatic CPS that preoperatively received either LEV or no anticonvulsant medication.

**Methods:** Retrospective case review. Information obtained included signalment, duration of clinical signs, presence of neurologic abnormalities before surgery, preoperative bile acid and ammonia concentrations, diagnostic imaging modality, duration of hospitalization, postoperative complications including seizures, and discharge status. Bayesian Poisson regression was used to estimate the risk of seizures in LEV-treated dogs when compared with untreated dogs.

**Results:** Levetiracetam was administered to 33% (42/126) of dogs. No dog treated with LEV experienced postoperative seizures, whereas 5% (4/84) of dogs not treated with LEV experienced postoperative seizures. The relative risk of seizures was significantly \( P < .0002 < 1 \) for the LEV-treated dogs, indicating LEV protection against development of postoperative seizures. No dog that experienced postoperative seizures survived to discharge from the hospital.

**Conclusions and Clinical Importance:** Levetiracetam administered at 20 mg/kg PO q8h for a minimum of 24 hours before surgery significantly decreased the risk of postoperative seizures and death in dogs undergoing surgical attenuation of extrahepatic CPS with ameroid ring constrictors.

**Key words:** Anticonvulsant drugs; Canine; Status epilepticus.

**Abbreviations:**

- ACD anticonvulsant drug
- CPS congenital portosystemic shunt
- LEV levetiracetam

**Postligation seizures have resulted in high-case fatality proportions in affected dogs.**

Administration of benzodiazepines, barbiturates (eg, phenobarbital, pentobarbital), and propofol, as either bolus treatment or constant rate infusions, have been described for treatment of status epilepticus after CPS ligation with limited success. Treatment with potassium bromide for 2 weeks before surgery has not been shown to decrease postligation seizure incidence. Tisdall et al reported that presurgical treatment with phenobarbital did not significantly decrease postoperative neurologic sequelae, but may have prevented development of generalized motor seizures or status epilepticus.

Levetiracetam (LEV) is a novel antiepileptic drug approved for treatment of partial-onset seizures in humans. It has also proved effective for treatment of simple partial, complex partial, and secondary generalized seizures, as well as status epilepticus. By binding to the synaptic vesicle protein SV2A, LEV is postulated to decrease the amplitude of late excitatory postsynaptic field potentials at the CA1 region of the hippocampus during repetitive stimulation and slow neurotransmitter release in a time- and concentration-dependent manner. LEV requires low frequency synaptic activity for entry into vesicles, but produces the largest reductions in excitatory postsynaptic field potentials at high frequencies. This property of LEV
causes the greatest efficacy of the drug to occur during rapid, pathological neuronal firing, as with seizures. In addition, LEV inhibits increases in intracellular calcium, delayed rectifier potassium currents, chloride-bicarbonate exchange, and AMPA receptors. Peak concentrations after oral administration in dogs occur 0.6 hours after administration of the first dose with minimal demonstrable adverse effects. Levetiracetam has been used successfully in dogs with refractory idiopathic epilepsy, and is one of a small number of ACDs recommended in humans with hepatopathy. As such, presurgical delivery of LEV in dogs with CPS would seem to have potential as a safe, effective means to prevent postligation seizures.

The purpose of this study was to retrospectively compare the incidence of seizures after the application of ameroid constrictors in dogs with extrahepatic CPS that were either treated preoperatively with LEV or with no ACD. We hypothesized that dogs receiving LEV before surgical shunt attenuation would have a decreased risk of developing seizures postoperatively.

**Materials and Methods**

**Case Selection**

Electronic medical records of dogs admitted between January 2003 and November 2010 to Texas A&M University’s Veterinary Medical Teaching Hospital (TAMU-VMTH) were searched for the keywords ameroid constrictor and portosystemic shunt ligation. To be included in the study, the presence of a single, extrahepatic portosystemic shunt confirmed by abdominal ultrasound examination, nuclear scintigraphy, or suggested by a clinically relevant increase in serum bile acid or ammonia concentration had to be documented in the record of each dog. Dogs must have undergone surgical application of an ameroid constrictor to attenuate the shunting vessel with complete surgical reports available for review. Dogs that met these inclusion criteria were divided into 2 groups: (1) those that received no ACDs before CPS ligation, and (2) those treated with LEV at least 1 day before CPS ligation. Dogs that received other presurgical ACDs were excluded from analysis.

For dogs treated with LEV before surgery, the dose, frequency, duration, and route of administration, must have been recorded. The presence of seizure activity was determined by evaluation of intensive care unit (ICU) records documenting the presence or absence of seizure activity for a minimum of 48 hours after surgery.

**Procedures**

Age, sex, breed, duration of hospitalization, and status at discharge (alive, dead, or euthanized) were recorded for each case. Data regarding the duration of clinical signs before surgery, the presence of preoperative neurologic abnormalities, and the presence of preoperative seizure activity was recorded for each dog. Preoperative concentrations of bile acids and ammonia were recorded for dogs having either of these tests performed. The imaging modality used for identification of the single extrahepatic CPS and the location of the shunting vessel were recorded.

For dogs receiving LEV before surgery, the duration of administration and total dosage administered in mg/kg/day was recorded. After surgery, the presence or absence of postoperative seizures was noted. For those animals with documented seizure activity, the number of seizures before discharge, death, or euthanasia, and the seizure type (generalized convulsive, generalized nonconvulsive, simple partial, complex partial) were recorded. The time from termination of the surgical procedure to onset of seizure activity was calculated in hours. All ACDs administered to attempt suppression of postoperative seizure activity and whether suppression of seizures was accomplished or not were recorded.

**Statistical Analysis**

The primary objective of this study was to determine whether LEV decreased the risk of postoperative seizures in dogs undergoing surgery for attenuation of single extrahepatic CPS. Descriptive and inferential statistical methods were used to describe the population of dogs, and to compare dogs that received LEV and those that did not. For descriptive purposes, continuous data were summarized by means of medians and ranges (ie, minimum and maximum values), and categorical data were summarized by means of contingency tables or proportions. For comparisons of dogs that received LEV with dogs that did not receive LEV, the Wilcoxon rank sum test was used for continuous variables, and chi-squared or Fisher’s exact tests were used to compare categorical data. All analyses describing and comparing LEV-treated and untreated dogs were performed by S-PLUS statistical software; a significance level of $P < .05$ was used.

Using standard frequentist methods, the relative risk of seizures in dogs not treated with LEV relative to those treated with LEV could not be defined, because the risk in LEV-treated dogs was 0. Thus, Bayesian Poisson (or log-linear) regression, as described by Ntzoufras, was used for analysis. Briefly, the model employed Bayesian inference, with vague or flexible prior beliefs, and a Markov chain Monte Carlo (MCMC) implementation. The MCMC implementation was performed by OpenBUGS version 3.1.2. The initial 5,000 iterations were discarded to allow for convergence, and the next 20,000 iterations were sampled for the posterior distribution. Observing convergence of 2 chains with widely different initial values checked convergence to the posterior distribution. The Bayesian estimate was taken as the posterior median of the parameter, and the 95% credible set was obtained from the posterior distribution quantiles. The $P$-value was defined as the probability of the relative risk being $<1$ in the posterior distribution.

**Results**

During the time period evaluated, 176 dogs had ameroid constrictors surgically applied for attenuation of CPS. Of these 176 dogs, 50 dogs were treated with ACDs other than LEV, including phenobarbital and potassium bromide, before shunt attenuation, and were excluded from the study population. A total of 126 dogs met the inclusion criteria for the study population. Of these dogs, 42 dogs received LEV and 84 dogs received no ACD before undergoing CPS attenuation. All 42 dogs receiving LEV were admitted during 2007 or later, whereas only 45% (38/84) of the dogs that did not receive LEV were admitted during 2007 or later; this difference was statistically significant ($P < .0001$). The median duration of LEV treatment before surgery was 6.5 days (range, 1–210 days). The median dose was 60 mg/kg/day (range, 30–83 mg/kg/day). Information regarding the duration of treatment with LEV postoperatively was available for 39 dogs.
The median duration of postoperative LEV treatment was 33 days (range, 0–99 days).

A large variety of breeds were represented in the study population. The predominant breeds represented were Yorkshire Terriers (39/126), Miniature Schnauzers (29/126), Pugs (8/126), Chihuahuas (7/126), mixed breed dogs (6/126), Dachshunds (5/126), Bichon Frises (5/126), and Miniature Poodles (5/126). Fourteen other breeds with fewer than 5 individuals undergoing CPS attenuation were included in the study. The distribution of breeds was similar between the LEV-treated and LEV-untreated dogs.

The age, sex distribution, duration of clinical signs before surgery, presence of preoperative neurologic deficits including seizure activity, preoperative bile acid and ammonia concentrations, location of shunting vessel, and duration of hospitalization did not differ significantly between the LEV-treated and the LEV-untreated groups (Tables 1 and 2).

The severity of preoperative neurologic deficits ranged from mild lethargy and ataxia with occasional head pressing to behavioral changes and generalized convulsive seizures. Although the difference was not significant (P = .1097), the proportion of dogs with neurologic dysfunction among those that received LEV (33/42; 79%) was greater than that of dogs which did not receive LEV (52/83; 63%).

Blood ammonia concentrations ranged from 9 to 741 μg/dL (median, 162 μg/dL). The ammonia concentration tended to be higher among animals receiving LEV (median, 196 μg/dL; range, 20–741 μg/dL) than in the dogs not treated with LEV (median, 127 μg/dL; range, 9–686 μg/dL), but this difference was not significant (P = .0509). Shunt location was reported in 122/126 dogs. A portocaval shunt was reported in 78 dogs (64%), and a portoazygous shunt was reported in 44 (36%) dogs. Although the difference was not significant (P = .0841), the proportion of dogs in the LEV group that had portoazygous shunts (20/42; 48%) was greater than that for the non-LEV group (24/80; 30%).

The most common imaging method for visualization of extrahepatic CPS was ultrasonography; the technique was used alone in 83 (66%) of study dogs, and in combination with either scintigraphy (14 dogs, 11%), portography (1 dog), or both (1 dog). Scintigraphy was performed alone in 25 dogs (20%), and an exploratory laparotomy was the method for diagnosis in 2 dogs. Significantly fewer dogs receiving LEV (5%, 2/42) had scintigraphy as a diagnostic modality (P < .0001) than dogs not receiving LEV (46%; 39/84).

The presence of postoperative complications was reported for 123 dogs; 38 dogs (31%) experienced postoperative complications. The most common complications reported were ascites (n = 5 dogs; 1 receiving LEV), diarrhea (n = 4; 3 receiving LEV), and vomiting (n = 4; 3 receiving LEV). Four dogs experienced seizures postoperatively; no dog that experienced postoperative seizures received LEV before surgical attenuation of CPS.

Four of 126 (3%) dogs failed to survive to discharge because of postoperative euthanasia. All dogs that failed to survive to discharge experienced postoperative generalized motor seizures. Seizures were observed between 15 and 56 hours postoperatively. Seizure activity in all dogs was described as generalized motor seizures. Three of 4 dogs that experienced postoperative generalized motor seizures underwent progression to status epilepticus, which was refractory to anticonvulsant drug treatment. Two dogs each experienced 2 generalized motor seizures before manifestation of status epilepticus; suppression of initial seizure activity in these dogs was accomplished by administration of diazepam IV as a bolus before progression. One dog experiencing postoperative seizures was refractory to all anticonvulsant treatment administered from the time of seizure onset, and experienced rapid progression to

Table 1. Comparison of continuous variables between dogs treated with levetiracetam (LEV) and untreated dogs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>LEV-Treated, Median (Range)</th>
<th>Untreated, Median (Range)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1 (0.25–8), N = 42</td>
<td>2 (0.25–11), N = 84</td>
<td>.5069</td>
</tr>
<tr>
<td>Duration of clinical signs (weeks)</td>
<td>8 (1–72), N = 40</td>
<td>6 (0–372), N = 75</td>
<td>.7439</td>
</tr>
<tr>
<td>Bile acids (μmol/L)</td>
<td>200 (55–336), N = 12</td>
<td>219 (37–686), N = 30</td>
<td>.6559</td>
</tr>
<tr>
<td>Ammonia (μg/dL)</td>
<td>196 (20–741), N = 38</td>
<td>127 (9–686), N = 48</td>
<td>.0509</td>
</tr>
<tr>
<td>Duration of hospitalization (days)</td>
<td>5 (3–15), N = 42</td>
<td>5 (3–24), N = 84</td>
<td>.7676</td>
</tr>
</tbody>
</table>

*P-value for Wilcoxon rank sum test comparing distribution between populations.

Table 2. Comparison of categorical variables between dogs treated with levetiracetam (LEV) and untreated dogs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>LEV-Treated</th>
<th>Untreated</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female intact</td>
<td>11/42 (26%)</td>
<td>23/84 (27%)</td>
<td></td>
</tr>
<tr>
<td>Female spayed</td>
<td>15/42 (36%)</td>
<td>26/84 (31%)</td>
<td></td>
</tr>
<tr>
<td>Male castrated</td>
<td>5/42 (12%)</td>
<td>18/84 (21%)</td>
<td></td>
</tr>
<tr>
<td>Male intact</td>
<td>11/42 (26%)</td>
<td>17/84 (20%)</td>
<td></td>
</tr>
<tr>
<td>Preoperative neurologic deficits</td>
<td></td>
<td></td>
<td>.1097</td>
</tr>
<tr>
<td>Present</td>
<td>33/42 (79%)</td>
<td>52/83 (63%)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>9/42 (21%)</td>
<td>31/83 (37%)</td>
<td></td>
</tr>
<tr>
<td>Preoperative seizure activity</td>
<td></td>
<td></td>
<td>.2833</td>
</tr>
<tr>
<td>Present</td>
<td>13/42 (31%)</td>
<td>17/83 (20%)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>29/42 (69%)</td>
<td>66/83 (80%)</td>
<td></td>
</tr>
<tr>
<td>Shunt location</td>
<td></td>
<td></td>
<td>.0841</td>
</tr>
<tr>
<td>Portocaval</td>
<td>22/42 (52%)</td>
<td>56/80 (70%)</td>
<td></td>
</tr>
<tr>
<td>Portoazygous</td>
<td>20/42 (48%)</td>
<td>24/80 (30%)</td>
<td></td>
</tr>
</tbody>
</table>

*P-value for Wilcoxon rank sum test comparing distribution between populations.
status epilepticus. The final dog was noted to have only a single generalized motor seizure, and experienced complete resolution of seizure activity after administration of an IV bolus of diazepam. This dog was euthanized 10 days postoperatively because of sepsis associated with a gastrostomy tube placed to facilitate administration of food and medications.

No dog (0/4) experiencing postoperative seizures received LEV preoperatively. Among 42 dogs receiving LEV, none developed postoperative seizures, whereas 4 of 82 dogs (5%) that did not receive LEV developed postoperative seizures. Using Bayesian Poisson regression, the risk of seizures was significantly ($P < .0002$) < 1 for the LEV-treated dogs, indicating a significant protective effect against the development of postoperative seizures.

**Discussion**

Of the 126 dogs reported here that underwent surgical attenuation of single extrahepatic portosystemic shunts with am eroid constrictors between January 2003 and November 2010, 3% (4/126) developed postoperative seizures. This is similar to the prevalence of neurologic dysfunction after application of am eroid constrictors reported in 8/168 dogs in a recent retrospective study, and consistent with the prevalence reported in conjunction with other attenuation techniques.

The cause of postligation neurologic dysfunction, ranging in severity from nonprogressive ataxia to generalized motor seizures, in dogs with CPS remains unclear. Potential etiologies include decreases in endogenous inhibitory central nervous system benzodiazepine agonist concentrations and imbalances in excitatory and inhibitory neurotransmitters. No consistent pathologic or metabolic abnormalities have been noted in dogs experiencing postoperative neurologic dysfunction. Cortical necrosis and polioencephalomalacia are reported in dogs after shunt ligation and development of status epilepticus. These changes, however, are suggested to be secondary to seizure activity rather than being causative.

Preoperative treatment with ACDs has been previously suggested as a means to increase seizure threshold in dogs undergoing CPS ligation. In a retrospectively assembled population of dogs with surgical CPS, individuals treated with phenobarbital (31/89) did not have a significantly lower incidence of postligation neurologic dysfunction (2/31; 6%) compared with those not receiving treatment (9/58; 16%). This may have resulted from the mechanism of action of phenoobarbital, inadequate presurgical loading (5–10 mg/kg at induction), or the small population of dogs studied. Additional factors indicate that phenobarbital may not be an ideal choice for dogs undergoing CPS ligation. Administration may result in substantial adverse effects, including behavioral changes, sedation, polyphagia, polyuria, and hepatotoxicity.

Levetiracetam is a piracetam ACD that is advocated in critical or geriatric human patients because of its limited hepatic metabolism and primary renal excretion. The pharmacokinetics of LEV in healthy dogs, after administration of a single PO, IM, or IV dose, as well as after repeated PO dosing, have been reported. The currently proposed effective serum concentration of LEV is 5–40 μg/mL, but a therapeutic range has not been definitively established. Long-term toxicity data have confirmed that LEV is very safe in dogs, with dosages of 300 mg/kg/day resulting in a stiff, unsteady gait in 1 dog, salivation and vomiting in dogs receiving 1200 mg/kg/day, and no observed treatment-related mortalities or histopathologic abnormalities. In the study reported here, the only adverse events identified that might have been attributable to LEV were vomiting (3/42) and diarrhea (3/42). Dogs receiving preoperative LEV were significantly less likely to have postoperative seizures compared with those that did not receive ACDs. The median duration of LEV administration before surgery was 6.5 days. Several animals, however, were treated with LEV for only 1 day before undergoing CPS attenuation, which should be adequate to reach steady state serum blood drug concentrations. Unlike some of the traditional anticonvulsant treatments, absorption of LEV after PO administration is rapid, with peak plasma concentration occurring 0.62 hours after administration of the 1st dose. Maintenance of the suggested therapeutic plasma drug concentration is easily achieved by PO administration of LEV every 8 hours at a dosage of 20 mg/kg.

No reliable predictors of postligation seizures in dogs have been reported, although some potential risk factors have been identified. Several studies have identified a tendency for older dogs to be affected. No significant difference was observed in the distribution of animals treated with LEV before surgery when compared with those in the non-LEV group in this study. Tisdall et al described an increase in the incidence of postoperative neurologic dysfunction in dogs with portoazygous shunts when compared with portocaval vascular anomalies. All dogs experiencing postoperative seizures reported in this study were diagnosed as having portocaval shunts on diagnostic imaging, which was confirmed at the time of surgical attenuation. The proportion of animals with portoazygous shunts was greater in the LEV group (48%) when compared with the non-LEV group (30%), indicating that perhaps the animals in the LEV group were at higher risk for developing postoperative seizures. Preoperative neurologic dysfunction or seizures may also increase the risk for postligation seizures. In 1 report, 9 of 11 affected dogs were neurologically abnormal before surgery for CPS. Interestingly, 79% of dogs receiving LEV in our study had preoperative neurologic abnormalities compared with 65% of dogs not receiving ACDs ($P = .1097$). Although this difference
was nonsignificant, it indicates that there was no evidence that the significant effect of LEV was the result of LEV-treated dogs being at lower risk for postoperative seizure development than untreated dogs.

Bayesian statistics were utilized in this study to evaluate the significance of administration of LEV in preventing the development of postligation seizure activity. There has been growing interest in evidence-based medicine and, along with it, an increased use of Bayesian statistics in medical applications. Proponents of Bayesian analysis emphasize several advantages of Bayesian statistical approaches, especially in clinical science. The authors selected and performed one specific Bayesian analysis largely because of the utility for Bayesian statistics when evaluating prognostic factors in small samples of hospital patients. Bayesian inference, as implemented by MCMC, can produce full posterior distributions without fear of violating assumptions such as normality (Gaussian distribution), even for very small samples. We used the approach to evaluate an extreme distribution observed in a small number of patients. In clinical science, other advantages include that Bayesian results can apply to patients, whereas frequentist results have only a population-based inference.

The major limitation of this study was its retrospective nature. During the time period evaluated, the primary imaging modality utilized for diagnosis of portosystemic shunt changed from nuclear scintigraphy, which was commonly utilized before 2007 alone or in combination with abdominal ultrasound examination, to ultrasound examination which was the predominant imaging technique in use during the later years evaluated. All dogs that received LEV were admitted during 2007 or later. Although the surgical technique for shunt attenuation remained consistent with all patients evaluated, there may have been differences in preoperative treatment, anesthetic protocols, and postoperative management that could have altered the incidence of postoperative seizures and deaths.

Another important limitation of this study is that information regarding dogs treated with ACDs other than LEV was not included in this study. We chose not to analyze these dogs because the number of dogs treated with other ACDs was small, and protocols for use of other ACDs were heterogeneous. This heterogeneity of treatment regimens may be attributable to the absence of evidence of clinical efficacy of other ACDs (eg, phenobarbital, potassium bromide) to prevent seizure activity after CPS attenuation, and concerns about the hepatotoxicity of these agents. A study to compare the efficacy of LEV with other ACDs to decrease the incidence of postoperative seizure activity may not be feasible because of the large sample size that would be required for a cohort study and the time period that would be required to obtain sufficient numbers of seizure cases to test the hypothesis of an association between LEV treatment and decreased incidence or odds of seizures.

Our study identified a low incidence of postoperative seizures (3%) in dogs undergoing surgical attenuation of CPS with ameroid ring constrictors. All dogs manifesting seizure activity after CPS surgery were ultimately euthanized before hospital discharge. No dog administered LEV at a minimum of 24 hours before surgery experienced postoperative seizures regardless of age at the time of surgery and location of the shunting vessel. Our results indicate that pretreatment of dogs with surgical CPS with LEV at a dosage of 60 mg/kg/day may decrease the incidence of postoperative seizures and status epilepticus.

Footnotes

* Keppra, UCB Inc, Smyrna, GA

S-PLUS statistical software, Version 8.1, TIBCO, Inc, Seattle, WA

References


