Successful use of intravenous and oral levetiracetam in a goat to control refractory seizures secondary to suspected polioencephalomalacia

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OBJECTIVE
To assess the clinical efficacy and plasma concentrations of levetiracetam in a goat with seizures.

ANIMAL
A 5-month-old doeling.

CLINICAL PRESENTATION, PROGRESSION, AND PROCEDURES
The goat was referred because of progressive anorexia and lethargy over 3 days. Clinical signs consisted of weakness, obtundation, opisthotonos, anisocoria, and cortical blindness. Initial evaluation was most consistent with polioencephalomalacia.

TREATMENT AND OUTCOME
Neurologic improvement occurred within 4 hours of thiamine administration, with appetite returning over 12 hours. On day 3 of hospitalization, the goat suffered acute onset repetitive seizures that were incompletely responsive to standard interventions over 3 hours. Administration of IV levetiracetam (60 mg/kg) produced resolution of seizure activity within 20 minutes. Levetiracetam was continued twice daily IV, then PO after day 6. Plasma concentrations were above or within therapeutic ranges (5 to 45 μg/mL) as previously established for other species, following both IV and PO levetiracetam. Oral administration (60 mg/kg, PO, q 12 h) resulted in plasma levetiracetam concentrations of 48.1 μg/mL 2 hours after a dose and 23.4 μg/mL 2 hours prior to the next dose.

CLINICAL RELEVANCE
Levetiracetam is a newer anticonvulsant commonly used in humans and small animals due to its efficacy, cost, and wide safety margin. Its use has not previously been reported in domestic small ruminants. In this case, levetiracetam showed excellent clinical efficacy in the face of refractory seizures, with no apparent side effects. Plasma concentrations during oral administration were at the high end of the therapeutic range, indicating absorption in a nonmonogastric species. Further studies are warranted to determine optimal dosing in small ruminants.

Keywords: levetiracetam, goat, seizure, polioencephalomalacia, small ruminant

History
A 5-month-old 14-kg crossbred doeling was referred because of progressive lethargy and inappetence of 3 days’ duration. The goat had been purchased 5 days prior to presentation and, upon integration to the new herd, was chased away from feed by the other goats. The goat became progressively hyporexic and lethargic. Tulathromycin and flunixin meglumine were administered with no improvement. By the morning of presentation, the goat was weak, anorexic, and mildly bloated.

Diagnostic Findings and Interpretation
Upon admission, the goat was dull but responsive to stimuli and in lateral recumbency with opisthotonos. Rectal temperature was 38.4 °C (reference interval [RI], 38.5 to 39.7 °C); heart rate, 100 beats/min (RI, 70 to 80 beats/min); and respiratory rate, 20 breaths/min (RI, 15 to 30 breaths/min). Capillary refill time was prolonged at 3 seconds. Palpebral, pupillary light reflexes (bilateral and consensual) and menace response were absent bilaterally. The abdomen was...

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the course of the 20-minute bolus of levetiracetam, phenobarbital was considered but not utilized because the interval between seizures became shorter. Focal and general interventions decreased the severity and duration of seizures but did not resolve them. Focal and general treatments included midazolam (0.2 mg/kg, IV, 2 additional doses), thiamine (10 mg/kg, IV, in 20 mL of 0.9% NaCl), dexamethasone (0.1 mg/kg, IV, once), mannitol (1 g/kg, IV), and a midazolam constant rate infusion titrated up to 0.12 mg/kg/h. These interventions decreased the severity and duration of seizures but did not resolve them. Focal and generalized cluster seizure activity continued, and concerning the interval between seizures became shorter. Phenobarbital was considered but not utilized because of its high cost and variable oral bioavailability in ruminants were it to be required long-term. Thus, levetiracetam (60 mg/kg, slow IV) was administered. The dose was based on those used for acute seizure control in small animals and foals and reported long-term oral efficacy and safety in an adult cervid. Over the course of the 20-minute bolus of levetiracetam, tonic-clonic seizure signs resolved. Following the postictal stage, no seizures reoccurred and the goat became responsive. Levetiracetam was continued IV twice daily on the basis of clinical assessment, and the goat became alert and appertent. Cefiotrof sodium (2.2 mg/kg, IV, q 12 h) was added for gram-negative coverage of potential aspiration during the acute repetitive seizures. Cefiotrof was utilized by an extralabel route (IV) to minimize potential seizure-inducing stimuli (IM injection) and for an extralabel indication (aspiration pneumonia).

On the morning of day 6, levetiracetam at 30 mg/kg IV and 40 mg/kg PO were administered concurrently for transition to oral administration. After this, levetiracetam (60 mg/kg, PO, q 12 h) was continued until day 21. No further seizure activity occurred for the remainder of hospitalization, and the goat was discharged on day 9. Follow-up was conducted by phone on days 17, 21, and 45. The goat remained bright and interactive, with a good appetite. Visual acuity was reportedly difficult to quantify, but the goat was able to climb rocks in the pasture and navigate its environment without difficulty. There were no reported changes upon discontinuation of levetiracetam. By day 45, the goat had grown appropriately and, although no ophthalmologic examination had been performed, there was no evidence of residual blindness.

Plasma was saved for evaluation of levetiracetam concentrations at times when venipuncture was clinically indicated. Blood was collected into heparin tubes, immediately centrifuged, plasma separated, and stored at −80 °C before analysis by high-performance liquid chromatography at Michigan State University Veterinary Diagnostic Laboratory. Plasma levetiracetam concentration was 96.9 μg/mL at 45 minutes after IV administration (day 2). During PO levetiracetam administration, concentrations were 23.4 μg/mL 10 hours after dosing (day 7) and 48.1 μg/mL 2 hours after dosing (day 9). The therapeutic range for humans is 5 to 45 μg/mL.

**Treatment and Outcome**

Thiamine hydrochloride (10 mg/kg, IV, q 12 h in 20 mL of 0.9% NaCl) was initiated as the treatment of choice for PEM. Intravenous fluid therapy with Plasma-Lyte A (60 mL/kg/d) was administered over the first 36 hours to correct the dehydration and azotemia. The goat was started on potassium penicillin G (22,000 IU/kg, IV, q 6 h) to provide coverage for potential listeriosis and pantoprazole (1 mg/kg, IV, q 24 h) for abomasal ulceration prophylaxis. Four hours after initial thiamine administration, the goat was ambulatory and appertent. Pupillary light and palpebral reflexes returned over 24 hours, although menace response remained absent. After initial IV administration, thiamine was continued SC to prolong duration of action (10 mg/kg, SC, q 12 h). On day 2, 30 mL of rumen fluid from a donor cow was transfused to assist with restoration of microbiota.

On day 3, 48 hours after admission, the goat was heard vocalizing and found unresponsive in a generalized tonic-clonic seizure. Midazolam (0.2 mg/kg, IV) halted seizure activity. Physical examination, venous electrolytes, and blood ammonia were unremarkable aside from hyperthermia (39.8 °C; RI, 38.5 to 39.7 °C) and hyperlactatemia (6.3 mmol/L; RI, < 0.4 mmol/L). Within 10 minutes of midazolam administration, generalized seizures lasting 15 to 120 seconds reoccurred at between 5- and 45-minute intervals over the course of 3 hours. During this time, therapies included midazolam (0.2 mg/kg, IV, 2 additional doses), thiamine (10 mg/kg, IV, in 20 mL of 0.9% NaCl), dexamethasone (0.1 mg/kg, IV, once), mannitol (1 g/kg, IV), and a midazolam constant rate infusion titrated up to 0.12 mg/kg/h. These interventions decreased the severity and duration of seizures but did not resolve them. Focal and generalized cluster seizure activity continued, and concerning the interval between seizures became shorter. Phenobarbital was considered but not utilized because of its high cost and variable oral bioavailability in ruminants were it to be required long-term. Thus, levetiracetam (60 mg/kg, slow IV) was administered. The dose was based on those used for acute seizure control in small animals and foals and reported long-term oral efficacy and safety in an adult cervid. Over the course of the 20-minute bolus of levetiracetam, tonic-clonic seizure signs resolved. Following the postictal stage, no seizures reoccurred and the goat became responsive. Levetiracetam was continued IV twice daily on the basis of clinical assessment, and the goat became alert and appertent. Cefiotrof sodium (2.2 mg/kg, IV, q 12 h) was added for gram-negative coverage of potential aspiration during the acute repetitive seizures. Cefiotrof was utilized by an extralabel route (IV) to minimize potential seizure-inducing stimuli (IM injection) and for an extralabel indication (aspiration pneumonia).

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**Comments**

Seizures are a common presenting complaint in sheep and goats, with PEM accounting for 46% of these, making the efficacy of levetiracetam in PEM-associated seizures important. Polioencephalomalacia was considered the most likely cause of this goat’s neurologic signs on the basis of evidence of a forebrain lesion (obtundation and cortical blindness) and initial rapid improvement in response to thiamine. Levetiracetam has gained popularity as an anticonvulsant in both human and veterinary medicine since gaining FDA approval in 1999. While benzodiazepines and phenobarbital are used IV for acute seizure control, limited long-term anticonvulsants exist for ruminants due to poor bioavailability after PO administration. Thus, demonstration of adequate absorption of PO levetiracetam in this ruminant in concert with clinical seizure control is of clinical relevance. Unlike most other anticonvulsants, levetiracetam is not a controlled substance; as such,
its utilization in food animal species as an alternative could be important. Side effects are generally mild, and it has a wide safety margin in a range of species. The most frequent veterinary side effects of nausea, vomiting, sedation, and ataxia were not observed in this goat. Although nausea is difficult to assess in animals and ruminants regurgitate normally, the goat retained an excellent appetite and chewed cud appropriately. Behavioral changes of increased anxiety or placidity are reported but were not noted in this case. As many goats are closely monitored companions, these potential side effects should be discussed with clients. Dose range and frequency vary depending upon the patient's seizure threshold, and as such, levetiracetam has a wide therapeutic range of 5 to 45 ug/mL. Initial loading dose is commonly 60 mg/kg IV with maintenance doses falling within the range of 20 to 60 mg/kg, 2 or 3 times daily. Plasma concentrations in this case suggest that a dose lower than 60 mg/kg would be sufficient in goats. However, only 3 time points were measured and variability may exist; thus, therapeutic drug monitoring is encouraged. Of particular interest, in this goat, during PO administration a dose of 60 mg/kg twice daily appeared to be adequate to maintain plasma concentrations within the therapeutic range. In other species, dosing 3 times daily is often required to maintain therapeutic plasma concentrations. With respect to PO administration, potential differences in absorption from the ruminant forestomach versus monogastric species may allow for twice-daily dosing, as supported by this case and in 1 adult cervid. Although only 5 months old, this goat was fully weaned and ruminating. The Food Animal Residue Avoidance Databank was contacted and unable to provide recommendations for milk or meat withdrawal for levetiracetam. Thus, there was documentation stating that the goat should not enter the production chain. Ceftiofur was chosen to broaden antimicrobial spectrum of coverage for aspiration pneumonia and administered IV to reduce seizure-inducing stimuli.

This was the first report of use of levetiracetam for seizure control in a goat. In this case, levetiracetam was highly efficacious, with no apparent clinical side effects and adequate plasma concentrations as comparatively described in other species. Further pharmacokinetic studies are indicated, as anticonvulsants are of clinical relevance in small ruminants.

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