Case Study Report

WIRES Central Coast Branch

Callie

The use of Levetiracetam in Macropod Seizure Syndrome

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Case Study for Potential Treatment of Macropod Seizure Syndrome

The purpose of this case study is to describe the use of Levetiracetam (100mg per 1mL) as an anti-epileptic in macropods with seizure syndrome. We postulate that seizure activity may be a transitional phase within the context of an acquired inflammatory or infective disease or developmental abnormality. Treatment of this transitional phase may improve survivability of the affected macropods, long after treatment is been ceased, enabling them to enjoy their normal life expectancy.

Call Sheet No: 1375803 (Night call number JP240401)

Species: Swamp Wallaby

Animal Nickname: Callie

Date admitted into care: 24.02.2020

Animal Age (presumed) at rescue: 183 days

Gender: Female

Background and current management:

Over the past 5 years, macropods in care in New South Wales have evidenced increasing seizure activity including Redneck wallabies, Swamp wallabies, Whiptail wallabies and Pademelons. Most of these macropods were in care for an extended period of time, exhibiting good health prior to the onset of the seizure syndrome. There is an increased prevalence of such seizure activity during the hot months of the year. In almost half the cases, the onset of seizures led to the demise of the macropod, despite intense input from both the carer and veterinarian support.

In the first phase of symptom onset, the macropod shows an increased tendency to spend more time in the pouch and there is increased vagueness, vocalisation and twitching. The macropod might also exhibit pyrexia, and slight limb tremor. In the second phase, the limb tremor develops into twitching and jerking movements and they develop a vague stare (potential absence seizure activity). Their gait is compromised and there is evidence of petit mal seizures. In the third and final phase, the symptoms progress rapidly to grand mal seizures which could last for hours unless treated. There is also a prolonged postictal phase after a major seizure.

Various treatments have been trialled with limited success. During the seizure, diazepam is administered to abort the seizure. In some affected macropods, treatment with a one-off steroid or meloxicam injection accompanied by a course of doxycycline for 10 days helped improve survival rate from 47% to 61% as per the Northern River WIRES branch data. [(1)]

Similarly, WIRES Central Coast branch have had numerous cases with increasing frequency, but sadly have had no success with reducing the fatality rate which was 100%.

Animal history:

Caller found joey alone in backyard at 18.25 on 24.04.2020 breathing heavily and shaking. The caller placed the joey in a basket to maintain warmth until collection. Anne Newman (Macropod Coordinator) accepted rescue at 18.37 on 24.04.2020 and collected the joey shortly afterwards. The joey was named Callie. She was alert but hypothermic on collection. Pam Strykowski (Macropod Carer) became the primary carer for the first month prior to transferring over to Maria Whitehead (Macropod Carer) for long term care on the 30.05.2020 for buddying with another swamp wallaby and eventual soft release within her facilities.

Animal husbandry:

Nutrition consisted of Wombaroo 0.7, grass, roots and Wombaroo Macropod pellets

Callie was paired up with a male swamp wallaby of similar age. She was initially housed in an indoor enclosure and taken outside on grass on a daily basis. She was eventually housed in an outdoor enclosure between 10am and 3pm to avoid the colder hours. Callie was moved permanently to the outdoor enclosure after 1 month in care. All indoor and outdoor facilities were equipped with CCTV for close monitoring of potential seizure activity.

Prior contributory health history:

Callie had intermittent loose motions from the first day. She developed severe diarrhoea after a few weeks in care but resolved after 5 days. This was complicated by skin dermatitis of her perineal area and tail. Her slow weight gain was of concern.

Onset of Seizure activity

First witnessed seizure: 16.07.2020 at 2130. Callie was out of her pouch alone which was unusual. Callie banged around the room in panic and seemingly uncoordinated. She lowered herself to the ground with her chest rubbing the mat and arms flopped sideways. She was tachypnoeic, avoided eye contact with a blank stare. She remained very jumpy with the slightest of noises. There was evidence of generalised hypertonia. She was restrained immediately.

She was taken to SASH (Specialised Veterinary Hospital Tuggerah) that evening by myself and Sally Milne (Macropod Carer). Her serum pathology including CK, toxoplasmosis and blood sugar was normal. The veterinarian administered 0.3mg/kg Diazepam STAT intramuscularly. Clindamycin 1ml / 12 hours was administered for 10 days. That evening Callie drank her feed and stayed in her playpen with Arlo (other wallaby) for the rest of the night. I monitored her temperature and general condition closely.

Suspected seizure: 27.07.2020 Callie refused her morning bottle though she ate her roots. She was cold and hypertonic. She potentially had a nocturnal seizure and was found in a post-ictal state. She was warmed up in a blanket and she slowly transitioned to her normal self. She later accepted her milk feed but sipped it very slowly. After consulting with Anne, Macropod coordinator, Critical Care nutritional supplement was added in each of her milk feeds to counter act the diarrhoea and weight loss.

Following consultation with Somersby veterinarians, it was decided to attempt novel therapy with oral Levetiracetam suspension for seizure prophylaxis. Callie was loaded with 50mg twice daily for 2 days and later maintained on 30mg twice a day. She remained seizure-free for 9 days.

Witnessed Seizure 9 days after starting Levetiracetam: Callie was fine in the morning, drank her feed and her on and off diarrhoea was settling. Callie was found hiding in a corner, very stiff and cold at 14.00 in what was likely a postictal phase. She was wrapped in a blanket, warmed up and placed in a pouch. She later suffered a witnessed seizure at 16.30, with sporadic limb jerking, tachypnoea, hyperextension of her head and generalised hypertonia. I administered Diazepam 0.27mls IM which aborted the seizure. Total length of seizure was 20 minutes.

In consultation with the veterinarian, the Levetiracetam dose was increased to 50mg three times a day. This regimen was continued for a month.

Weaning off the Levetiracetam

Callie remained seizure-free for over a month and the Levetiracetam was gently weaned off by 10mg a week. A total of 14 weeks were required to wean her off the Levetiracetam completely. During this time frame, she was kept in a supervised 150 m2 outdoor enclosure. She thrived and gained weight, reaching her physical and developmental goals consistent with her age. She did not show any evidence of side-effects from the Levetiracetam and remained seizure-free two months after ceasing the medication completely. She is now ready for definite release.

Levetiracetam Use

Levetiracetam is a very well tolerated anti-epileptic used in adult humans and children with idiopathic generalised epilepsy. It has a favourable low side effect profile and can be conveniently administered as an oral solution. It has excellent oral bioavailability. In children, the recommended starting dose is 10mg/kg twice daily but the dose can be increased to 60mg/kg depending on clinical response and tolerance. The common side effects described in humans (>10%) include lethargy, headaches and increased infection risk.

The major route of excretion in humans is via urine (95%). The mean plasm half life is 7 +/- 1 hours. Oral administration to pregnant rats in the early stages of gestation was associated with increased risk of embryonal mortality, skeletal variations and reduced foetal weight. The use of Levetiracetam in the late stages of gestation was not associated with any adverse developmental effects. Studies concluded that the risk of having an abnormal foetus as a result of Levetiracetam use, far outweighed the dangers to the mother and her offspring of uncontrolled epilepsy.

In animal models, Levetiracetam is not active in the classical screening models for anticonvulsants, however it induces potent protection in a broad range of animal models for partial and primary generalised seizures, with an unusually high safety margin between therapeutic doses and doses inducing adverse drug effects. Levetiracetam also displays potential antiepileptogenic properties by dose dependently inhibiting the **development of kindling**, after discontinuation of the active substance. [(2)]

Conclusions

No definite conclusion can be drawn from a single case study and it raises more questions than answers. The use and partial success of antibiotics like doxycycline and clindamycin raise the possibility of a transmissible infection being the culprit behind the seizures. The lack of any positive findings on previous post-mortem examinations and serology remains very elusive and unhelpful. It might be the case that an inflammatory state persists even after the infection is treated resulting in ongoing seizures after the infection is treated. This lowers the macropod's seizure threshold, hence requiring seizure prophylaxis for an extended period of time under close supervision.

Another possibility is that Levetiracetam inhibits the development of kindling resulting in long term seizure free periods, long after ceasing the medication. Kindling is the tendency of some regions of the brain to react to repeated low-level electrical stimulation by progressively boosting electrical discharges, thereby lowering seizure thresholds. In other words, repeated seizure activity increases the risk of the macropod developing more seizures because of increased neuronal sensitisation. The use of Levetiracetam for a given period of time potentially breaks this vicious cycle (kindling) resulting in long term seizure free living in the wild without the need for long term Levetiracetam administration.

Limitations and future studies

Ideally, Callie's success story is followed by monitoring in the wild via a GPS device but this is very labour intensive and financially prohibitive.

This is a single case study and the use of Levetiracetam in macropods with seizure syndrome deserves a double-blind, placebo controlled, interventional study to better elucidate both its efficacy and safety. We hope that this study might encourage other carers and veterinarians to trial this novel approach.

References

1. Presentation of the undiagnosed Macropod Seizure Syndrome. WIRES Northern Rivers Branch
2. Monthly Index of Medical Specialities

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