NeuroNews

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Status epilepticus

- a couple of recent developments

NeuroNews is an informal, but hopefully informative, newsletter covering a range of clinically relevant neurological topics. Cases detailed in these articles are patients kindly referred to me by veterinarians in South Australia or western Victoria/NSW.

Status epilepticus (SE) has been defined as continuous seizure activity lasting longer than thirty minutes. However at the coalface of clinical practice, it may be more realistically described as seizure behaviour in excess of five minutes duration, or repeated seizures with no regaining of consciousness between ictal events.

At the recent ECVN/ESVN symposium, which I attended last month, two papers were presented which detailed some interesting developments with respect to SE in small animals, which may be of interest.

AETIOPATHOGENESIS

It is thought that SE develops as a result of a persistent paroxysmal depolarising shift, which induces protracted aberrant episodes of action potentials in neurones within the seizure focus. For reasons that are poorly understood, this activity is refractory to the normal processes that usually terminate seizure. However it is currently believed that it may relate to altered behaviour of GABA receptors and particularly a decrease in the inhibitory action of GABA(A) receptors.

In any event, the major concern in SE patients is the high risk of secondary brain injury as a result of a combination of factors, including an inability to meet the metabolic demands of the seizuring brain (especially glucose), hypotension and hypoxia, with the release of a range of neurotoxic substances.

Extracranial effects of SE may also be clinically significant, necessitating specific action. The production of high levels of catecholamines contributes to cardiovascular deregulation and risk of cardiac arrhythmia. Anaerobic metabolism in muscles during prolonged seizure typically leads to lactoacidosis. Hyperthermia and respiratory insufficiency are potentially life-threatening complications.

The neurological endpoint is reached when the above factors lead to inadequate brain perfusion and consequent neuronal death.

1- NON-CONVULSIVE STATUS EPILEPTICUS

Although the classical clinical picture in SE is one of persistent generalised seizure and disturbed consciousness, recent EEG-based research (*Mariani 2013*) has demonstrated the existence of a non-convulsive form of SE (NCSE), in

which motor activity is minimal or absent. The significance of this syndrome is that, although the patient may be exhibiting no obvious signs of seizure, profound and life-threatening metabolic disturbances are likely to exist.

NCSE is associated with a guarded prognosis in humans and initial evidence suggests that the situation is similar in dogs. However, it is believed that prompt recognition can improve outcomes. The author reported that some dogs responded to treatment with a single intravenous bolus of midazolam and others showed improvement following subsequent midazolam CRI. Nonetheless, the majority of dogs in this series died or were euthanased.

In clinical practice and in the absence of EEG, awareness of the possibility of NCSE on the basis of careful neurological assessment and comprehensive blood-work can only be of merit.

2- DELIVERY OPTIONS FOR BENZODIAZEPINES IN SE

The anticonvulsant properties of benzodiazepines largely stem from their ability to potentiate the effect of GABA in inhibiting the initiation of neuronal action potentials. It is known that the effectiveness of rectal administration of benzodiazepines in the prevention or treatment of SE is somewhat variable. This is believed to be determined in part by whether the drug is absorbed into the caudal and middle rectal veins, avoiding '"first pass" metabolism by the liver, or is absorbed into the cranial rectal veins which drain into the portal vein.

There is also evidence to suggest that rectal diazepam is more efficacious, as an anticonvulsant, than midazolam by the same route. However the use of compounded diazepam suppositories (at a dose of 2mg/kg) did not result in therapeutic levels of active agent.

Leading veterinary neurologist, Simon Platt, reported on his recent work trialling a novel midazolam gel formulated for intranasal administration. Results indicated that this preparation was more reliably absorbed nasally than the standard parenteral solution administered either rectally or nasally. In around eight minutes, a mean peak plasma midazolam concentration of 450ng/ml was achieved – more than double the level obtained through the nasal administration of a parenteral solution in a human study.

It is believed that, subsequent to nasal administration, therapeutic levels within the brain are achieved not only by passage across the blood-brain barrier following absorption into local capillaries, but also by direct passage into the CSF via the olfactory mucosa, avoiding the BBB.

The effectiveness of intranasal administration of midazolam is currently being investigated as part of a multi-institutional study.

I am delighted to assist with diagnostic investigation and management of refractory or severe seizures.

Best wishes,

Ian Douglas

NeuroVet, Palmer House, 1 Flinders Road, Bellevue Heights, SA 5050

PO Box 384, Balhannah, South Australia 5242

t (all hours) 0416 022178 **e** ian@neurovet.com.au w www.neurovet.com.au