



Seizures in Dogs - Part 3

By Dr. Filippo Adamo, DVM, Dipl. ECVN, Veterinary Neurology Specialist
President Bay Area VNN (Veterinary Neurology Neurosurgery Consulting)
208 Santa Clara Way, San Mateo, California, USA 94403 (608)334-3713



Flippadamo@yahoo.com

www.bayareavnn.com

See Issue 3 of 2011 (pages 120-121) for Part 1
See Issue 4 of 2011 (pages 116-117) for Part 2

Fig 1

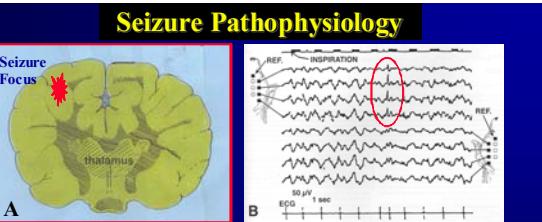


Fig A. The seizure focus (red spot) is the area of the brain where the abnormal electrical activity or paroxysmal discharge (PDS) originates.

Fig B. This abnormal electrical activity may be recordable on an EEG (spikes outlined by the oval red) even when the patient is not having seizures. In order to have the clinical manifestation of seizure, the neurons at the seizure focus they have to reach a critical number and they must to become synchronized into the paroxysmal firing.

B. Bromide (usually formulated as potassium bromide).

- Bromide is one of the initial drugs of choice for dogs. It is also added to the Phenobarbital when the seizures are not adequately controlled despite having the Phenobarbital blood level in the high end of the therapeutic range. However, in now days other new antiseizure medications such as Zonisamide or Levetiracetam (Keppra) are used as add on medication to the Phenobarbital instead of bromide (see below). This because the association of Phenobarbital and bromide may increase the side effects of both drugs and negatively affecting the dog quality of life.
- Mechanism of action: Bromide are negative charges with the tendency to get across the neuron cell membrane (trough the Cl- channel) and accumulate in side the neuron. They have a synergic action with Phenobarbital because while the Phenobarbital keeps opens the Cl-channel, the Br-ions enter inside the cells by competing with the Cl- channel. Because overall Br- has more negative charge than the Cl-ions, the end result is more negative charge inside the neuronal cells which make the cells more stable.
- Bromide is eliminated by the kidney and it is the preferred antiseizure drug for patients with liver disease.
- Three - 4 months are required to reach a steady concentration in the blood. This way serum level should be checked 2-3 weeks after initiating therapy or changing the dose.
- Recommended therapeutic serum level: 1-3mg/ml, when used as monotherapy, 1-2mg/ml when used as add on to the Phenobarbital.
- Cost: inexpensive
- Adverse effects:
 - Similar to the Phenobarbital: sedation, ataxia,

increase in eating, drinking and urinating are common dose dependent side effects.

- Pelvic limb stiffness and hind leg weakness is often evident.
- Hyperactivity, pruritic skin rash and aggressiveness have been reported
- Gastro-intestinal upset. Because of its irritative action of on the gastro-intestinal mucosa, potassium bromide should be administered with food.

h. Doses:

- Maintenance 30-35 mg/kg orally every 24 hours or divided twice daily. This dose usually follows the loading dose. Otherwise, it may take 2-3 months before having the benefit from the therapy
- Loading dose: 400-600 mg/kg orally divided 1.24 hrs loading dose: 100 mg/kg every 6 hrs for a total of 4 doses. This patient should be hospitalized for this loading procedure.
- Five days loading dose: 450 mg/kg of potassium bromide is dived over 5 days (90 mg/kg/daily). The maintenance (35 mg/kg/day) dose is added to the daily loading dose for each of the 5 days (125 mg/kg/day). This dose should be divided twice daily to avoid gastro-intestinal upset. On day 6, the maintenance dose is started.
- Serum bromide level is checked one week after loading and, then 1 month and 3 months later after starting the maintenance dose.

C. Diazepam, Midazolam:

- They should be used only in emergency situation and to stop the status epilepticus in dogs.
- Mechanism of action: similar to the Phenobarbital (binds to its own binding sites on the GABA receptor, and opens the channel to Cl-). However it is much more effective because it reach the nervous system very quickly; however it is also eliminated very quickly as well. This why when used to stop the status epilepticus requires multiple intravenous administration or a continuous rate of infusion.
- Doses:
 - Diazepam
 - 0.5-1 mg/kg/IV bolus for seizures
 - 1-2 mg/kg per rectum
 - 0.5-2 mg/kg/hr continuous IV rate infusion
 - Midazolam
 - 0.25 mg/kg IV bolus
 - 0.25 mg/kg/hr continuous rate infusion

4. Second-Line Antiseizure drugs.

A. Zonisamide (Zonegran);

- Zonisamide is the most common drugs used as add on to the Phenobarbital therapy when this becomes ineffective.
- Pharmacology:
 - Exact mechanism unknown - possible decreased activity of Na+ channels
 - Majority excreted in urine; about 20% hepatic metabolism

- concentration in the blood.
- c. Cost: it used to be very expensive, but the current generic formulation decreased significantly its cost.
 - d. Adverse effects:
 - i. Sedation, ataxia, inappetence
 - e. Doses: 8-12 mg orally every 12 hr
 - f. Therapeutic range: 10-40 mg/ml
- B. Levetiracetam (Keppra)**
- a. Pharmacology:
 - i. Unclear anticonvulsant mechanism
 - ii. Prevents hypersynchronization of neurons and propagation of seizure activity? No effect on normal neuronal excitability.
 - iii. Mostly renal excretion
 - iv. Two days are required to reach a steady concentration in the blood.
 - v. Administration: PO; IV formulation became recently available
 - b. Cost: Moderate expensive; the current generic formulation decreased significantly its cost.
 - c. Adverse effects:
 - i. Minimal reported
 - ii. Behavior changes, GI upset
 - d. Doses: 20 mg/kg orally every 8 hr
 - e. Therapeutic range: 5.5-25 mg/ml

Felbamate and Gabapentin.

- D. Ineffective antiseizure drugs:** several antiseizure drugs used effectively in people including phenytoin, carbamazepine, and valproic acid are not effective in dogs because they are eliminated too quickly in this species.

E. HOME CARE FOR CLUSTER SEIZURES

Diazepam can be administered rectally to help in the management of cluster seizures at home. This treatment has been shown to decrease the number of cluster seizure events over a 24-hour period. The recommended dose is 1 mg/kg of diazepam administered at the onset of seizures, which can be given up to 3 times over a 24-hour period. Dogs receiving phenobarbital should receive a dosage of 2 mg/kg, as chronic phenobarbital therapy reduces mean peak benzodiazepine concentrations following the administration of rectal diazepam. Because diazepam is inactivated by light and adheres to plastic, it is best to dispense the drug in the original glass vial and instruct the owner to draw the required amount into a syringe when needed. A rubber catheter or teat cannula is then placed on the syringe for the rectal administration. Suppository forms of the drug are available, but the pharmacokinetics of these products has not been studied in dogs to support their use.

With the recent difficulties in obtaining injectable diazepam, questions have arisen regarding the efficacy of midazolam given rectally to control cluster seizures. This is not effective, as rectal administration of midazolam to dogs has been shown to result in very low system bioavailability of the drug.

Questions? Please post your question on TTRM forum.
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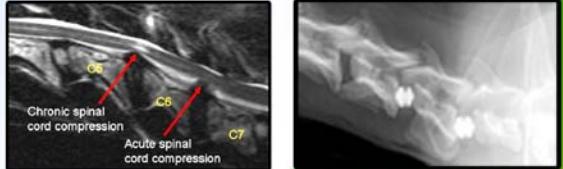
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If you have a patient that you believe might benefit from placement of an artificial disc or would like more information, please contact Dr. Filippo Adamo via email:

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