Seizures in younger dogs and cats

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INTRODUCTION

Seizure disorders are becoming more frequently diagnosed in younger dogs and cats in clinical practice; however there is a lack of definitive data about the real frequency. The specific development characteristics of younger animals have to be considered. The underlying cause of seizures has to be investigated with particular attention to congenital, degenerative or metabolic disorders and inflammatory/infectious diseases. Anti-epileptic treatment is recommended and should be started in addition to the treatment of the underlying disorder where present. For the purpose of this article, younger animals are defined as those less than six months old. This article will address the approach and treatment of younger dogs and cats with recurrent seizure activity.

THE YOUNGER BRAIN

Young animals have more permeable blood brain barriers than adults (Hellmann *et al.*, 1982). The consequence of this is a significantly increased risk of cerebral exposure to toxins, drugs and metabolites. Thus, the characteristic inquisitive behaviour of younger animals and the absence of a routine eating habit may increase the risk of neurotoxicosis.

The immature brain may also be more susceptible to seizures due to the changes occurring during natural development and maturation for two main reasons. Firstly, there is a decrease in the inhibitory neurotransmitter system (GABA) function relative to an overdeveloped excitatory system (glutamate) when compared with an adult brain (Young *et al.*, 1990; Fritschy *et al.*, 1994). The maturity of the inhibitory neurotransmitter GABA is crucial for the cessation of the seizure activity and to balance the glutamate excitatory system. Secondly, incomplete brain myelination (myelination begins in the last stage of gestation and continues for the first six months of age) contributes to the increase risk of seizures in the immature brain (Kubova *et al.*, 1994).

THE YOUNGER BODY

Drug use in younger animals requires special consideration of the organ systems responsible for drug metabolism and elimination.

Younger animals have a rapidly changing body weight and body surface area which has to be kept in mind when dosing anti-epileptic drugs (AEDs) whose dose is based on body weight, in order to avoid sub-therapeutic or toxic AED blood concentrations. The absorption of AEDs depends on the route of administration (oral or parenteral). The reduced GI absorptive capabilities of younger animals can lower the systemic AEDs serum level and efficacy (Boothe and Tannert 1992). The increase in percentage of body water content can affect the distribution of water soluble AEDs such as bromide. Younger animals have a lower serum protein concentration that can lead to an overdosage of protein bound AEDs (phenobarbitone and diazepam). Additionally, the immature liver is responsible for decreased metabolism of phenobarbitone, diazepam and gabapentin (one third of which is metabolised by the liver in dogs), leading to an increased risk of AED toxicosis. Finally, reduced renal clearance present in immature dogs can be particularly important when using the water soluble AEDs such as bromide and gabapentin.
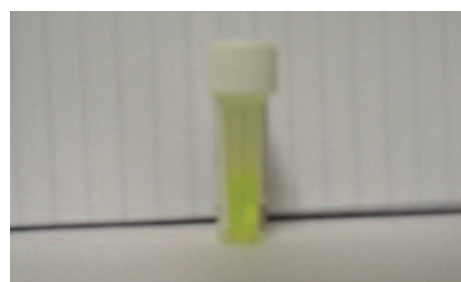

Fig. 1a: *FIP: Xantocromic CSF tap from a young DSH. The CSF analysis was suggestive of FIP infection: [WBC 391 mm3 (<5) of which ~ 80% neutrophils, RBC 0, Protein 8.62 g/l (<0.25)], IgG FIP CSF = 1:100, IgG FIP blood >1280. **

DIAGNOSTIC APPROACH

Although there is a lack of data in younger dogs and cats, the overall seizure incidence during the life time varies from 0.5 to 5.7% of all dogs and from 0.5 to 1% of all cats (LeCouteur and Child 1989). On evaluation of a patient with a history of seizures, it is necessary to evaluate the comprehensive history. Many of the seizure episodes are not witnessed by
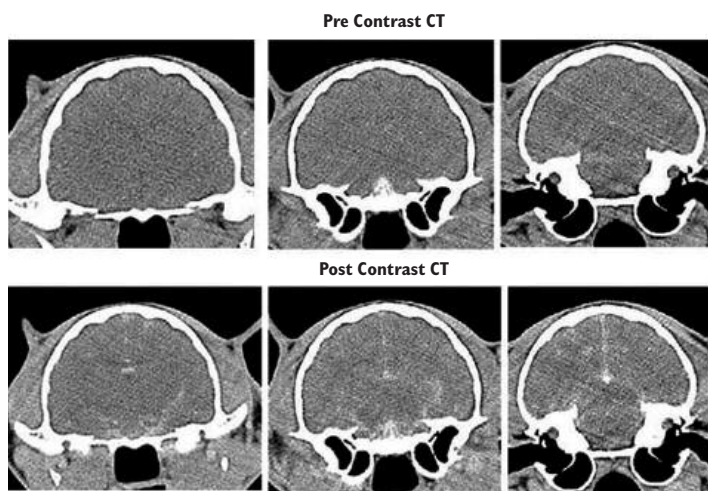
Pre Contrast CT

Post Contrast CT

Fig. 1b: *FIP: The CT study showed diffuse patchy uptake of contrast suggestive of meningoencephalitis.**

the veterinarian and can be confused by the owner with other 'events' such as syncope, narcolepsy/ cataplexy, vestibular and even behavioural disorders.
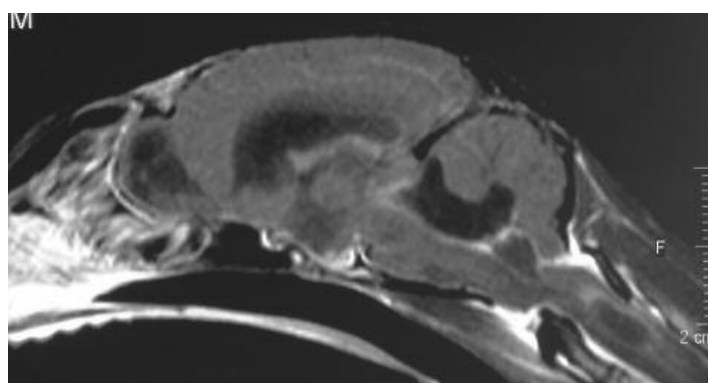

Fig. 2: *FIP: Sagittal post contrast T1W magnetic resonance image of 4 month old DSH cat with a PM diagnosis of CNS FIP. Lateral ventricles, mesencephalic aqueduct and fourth ventricles dilatation is visible; diffuse contrast uptake is present at the level of the ependymal layer (Ependymitis). **

Physical examination should be complete, with particular attention paid to the cardiorespiratory and gastrointestinal systems, and body temperature; palpation of the calvarium should be performed looking for open fontanelles. The examination of the eye is an essential part of the neurological examination in case of suspected intracranial diseases. The eyes are the 'window to the brain'; in fact the retina and the optic disc are the only directly visible part of the nervous system. In cases of neurological disease, the neuro-ophthalmological examination helps in localising the disease process, in detecting primary disease such as chorioretinitis (i.e. associated with inflammatory diseases) or secondary signs such as papilloedema resulting from increasing intracranial pressure (i.e. secondary to **meningo-encephalomyelitis of unknown aetiology** (MUA) or hydrocephalus or brain tumour).

An exhaustive neurological examination is mandatory. Idiopathic epileptic animals are usually neurologically normal in between seizures. However, animals with secondary seizures may have detectable neurological abnormalities in this inter-ictal period. In the immediate post-ictal period it is common to temporarily have so called 'post-ictal signs', i.e. blindness, behaviour changes, ataxia and lack of menace response.
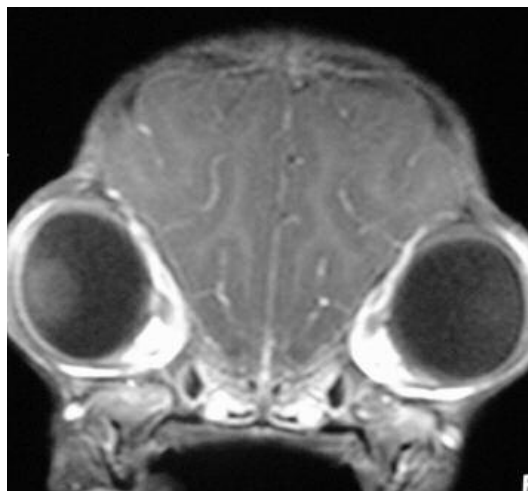

Fig. 3: *MUA: 4 month old female Chihuahua with seizures and multifocal CNS signs. CSF analysis was consistent with MUA. The MRI showing the characteristic signs of leptomeningitis (the so called 'ivy signs' in humans. The dog received only Cytarabine (50 mg/m2, sc q 12 h for 4 doses) repeated every 3 weeks. The dog is still on this protocol after 2 years without any more seizures.*

Younger animals are less likely than adults to suffer from idiopathic epilepsy and an identifiable cause of seizures should be carefully investigated (Podell *et al.*, 1995). The differential diagnosis in younger dogs and cats for seizure events should include metabolic disease, i.e. portosystemic shunt, juvenile hypoglycaemia (due to breed and or severe intestinal parasitism), as well as toxicity (Table 1). The initial diagnostic evaluation, following an isolated seizure episode, should include a haemogram, a biochemistry profile including serum glucose, cholinesterase (the poisonous effect of organophosphorous and carbamate pesticides comes about through the inhibition of cholinesterase) and lead level, urinalysis, and serum bile acids. Faecal examination should be part of the minimum database in younger animals, where an intestinal parasitic burden can induce anaemia, hypoglycaemia, and hypoproteinaemia and ultimately trigger seizure activity. Skull radiographs, and cerebral ultrasound through an open fontanel can help in identifying the presence of trauma and ventriculomegaly respectively. Cerebral MRI and cerebrospinal fluid (CSF) analysis are recommended to investigate intracranial congenital disorders, such as hydrocephalus or lissencephaly, inflammatory disease and congenital brain tumours even if rarely reported (Smith *et al.*, 2007). When infectious disease is suspected, additional tests to perform on CSF include PCR, titres and culture (Table 2). Additionally, blood and urine should be analysed for storage disorders if other tests have proven negative.

TABLE 1: Possible causes of seizures in puppies and kittens

Category of disease (VITAMIND)	Diseases/breed-related
Vascular	Haemorrhage due to coagulopathy (i.e. secondary to *Angiostrongylus vasorum*)
Infectious	
Virus	Any - see Table 2
Bacterial	Aerobe, anaerobe, abscess
Protozoal	Toxoplasmosis, Neosporosis, Encephalitozoonosis
Rickettsial	Erlichiosis, Richettsiosis, Anaplasmosis,
Fungi	Aspergillosis, Cryptococcus
Parasitic	Fleas, Coccidian, Hookworms, Larva migrans, *Angiostrongylus vasorum*
Inflammatory°	Meningoencephalomyelitis of Unknown Aetiology (MUA): GME, Breed related meningoencephalitis (Pug, Yorkshire Terrier, Maltese) Eosinophilic Meningoencephalitis, Periventricular Encephalitis
Toxic	Pesticides (Organophosphate,Carbamates, Pyrethroids, Metaldehyde) - Rodenticide (Bromethalin, Rotenone, Zinc Phosphate) - Herbicides - Ivermectin - Heavy Metals - Poison plants – Mycotoxins - Recreational drugs (Amphetamine, Cocaine, Marijuana) - Disinfectants - Antifreeze - Tetanus toxin - Slug bait (strychnine) - Metronidazole - Mycotoxin (spoiled dairy, bread and compost)
Trauma	Any (acute and chronic)
Anomalous	
Hydrocephalus	Bulldog, Chihuahua, Maltese, Lhasa Apso, Pomeranian, Toy Poodle, Pug, Pekinese, Boston Terrier, Siamese cat, Chihuahua, Yorkshire Terrier, English Bulldog, Cairn Terrier
Hydranencephaly/Poroncephaly	Secondary to infectious disease or congenital
Lissencephaly	Irish Setter, Lhasa Apso, Fox Terrier, DSH and Korat cat
Polymicrogyria	Poodle
Corpus Callosum agenesis	Labrador, DSH cat
Dandy-Walker syndrome	Not breed specific (puppies and kittens)
Caudal occipital malformation syndrome (COMS)	Cavalier King Charles Spaniel, Pug, Yorkshire Terrier, small brachycephalic breeds
Intracranial intra-arachnoid cysts	Not breed specific
Metabolic	
Portosystemic shunt -	Yorkshire Terrier, Maltese, Schnauzer, Irish Wolfhound, Old English Sheepdog,
Hepatic microvascular displasia	Poodle, Schnauzer, Dachshund, Yorkshire Terrier, Shih-Tzu, Cocker spaniel
Hypoglycaemia	Toy and miniature breed (severe parasites, inadequate diet, systemic infectious)
Hypoparathyroidism	Primary Hypoparathyroidism
Hypoxaemia	Neonatal asphyxia, cardiac or respiratory
Electrolytes imbalances	Any breed
Iatrogenic	Post anaesthetic hypoxia - Hyperthermia - Heat stroke (locked in the car) Post-Vaccine?*
Idiopathic-Inherited Epilepsy	Beagle, Belgian Tervuren, Bernese Mountain dog, Collie, Dachshund, Golden Retriever, Keeshound, Irish Setter, Labrador Retriever, Lagotto Romagnolo, Shetland, Vizsla, German Shepherd dogs, English Springer Spaniels
Neoplastic	Epidermoid and Dermoid Cyst, Medulloblastoma, Lymphoma
Nutritional	Thiamine deficiency, Hypocalcaemia
Degenerative	
Leukodystrophy	Labrador, Dalmatian, Shetland Sheepdog, Samoyed, Silky Terrier, Poodle, Scottish Terrier, Bernese Mountain dog, DSH
Glycogen storage diseases	Toy breeds Silky Terrier, DSH, Norwegian Forest cat
Spongiform Encephalopathy	Labrador, Saluki, Silky Terrier, Egyptian Mau cat
Lysosomal storage	German Shorthair Pointer, Portuguese Water Dog, Beagle, Alaskan Husky, DSH,
Mitochondrial encephalopathy	Siamese and Korat cat
Multisystemic Neuronal degeneration	Cocker Spaniel, Rhodesian Ridgeback
Ceroid Lipofuscinosis	Chihuahua, Dalmatian, English Setter, Dachshund, Saluki, Australian Cattle Dog, Border Collie, Siamese cat
Hereditary amblyopia	Irish Setter
Fucosidosis	English Springer Spaniel
Lafora's disease	Wire haired Dachshund, Poodle, Basset Hound

Red text: more common causes.

°Frequently seen in the author's experiences

*Anectodically reported association, however not well documented.

TABLE 2: CSF titres and/or PCR for most common infectious diseases

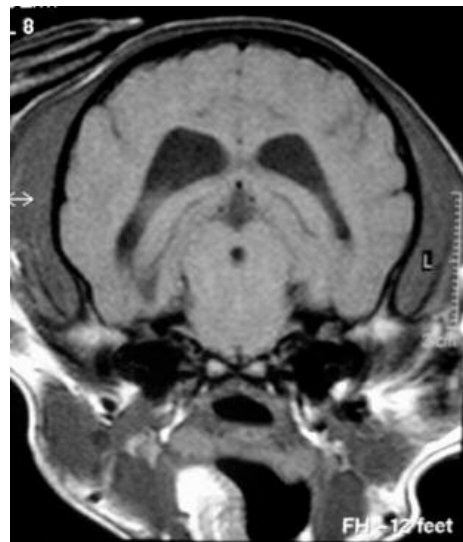| Puppies	Kittens
Toxoplasma gondii and *Neospora caninum*	*Toxoplasma gondii*
Distemper	Coronavirus
Parvovirus	Parvovirus
Herpesvirus	Herpesvirus
Adenovirus	Calicivirus
Bornavirus	Bornavirus
	FeLV/FIV

Fig. 4a: *Post vaccine seizures?: 12 week old male CKCS with a history of sudden generalised tonic clonic cluster seizures; he had received the last vaccination 2 weeks earlier. Haematology was consistent with antigenic stimulation [increase WBC 50.10 10x^9/L (6-16) with marked lymphocytosis 8.3 10 9/l (<5) and neutrophilia 24.70 10x^9/l (<13)]. Biochemistry, total bile acids, T4, urine analysis and abdominal ultrasound were unremarkable. CSF analysis: increase in protein 0.37 g/l (<0.25), RBC 466/ul, WBC 78/uk (<5) 70% activated lymphocytes and 30% macrophages. CSF RT-PCR was negative for infectious diseases. Magnetic resonance detected mild leptomeningeal uptake of Gadolinium in T1W post-contrast.*

Figs. 4b and 4c: *4b (pre-contrast T1WI) and 4c (post-contrast T1WI): A presumptive diagnosis of seizures secondary to antigenic stimulation (post vaccine?) was made. Charlie received a 50 mg/kg loading dose of Levetiracetam IV to control the seizures. Sequential haematological examinations showed a progressive normalisation of the values. He is still on levetiracetam without anymore seizures since the beginning of the treatment.*
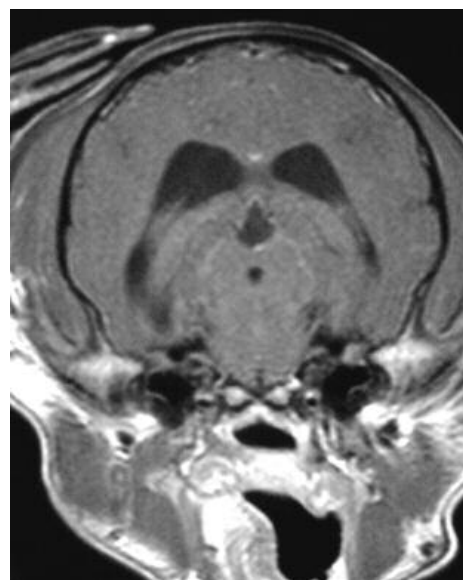

Fig. 4c.

Although seizures in younger dogs and cats are often secondary to an intracranial or extracranial disease, the possibility of an early manifestation of idiopathic epilepsy should not to be ruled out (Jokinen *et al.*, 2007; Hoskins 2001).

TREAT OR NOT TO TREAT?

Recurrent seizures can effect the brain's development. Accumulating human data suggests that neonatal seizures may be associated with or cause brain damage in the immature brain and increase the risk of subsequent seizure–induced injury, predisposing to epilepsy in adulthood. Moreover, the main factor that determines more persistent epilepsy, following on from early seizures, is protracted seizure episodes (Schimd *et al.*, 1999; McCabe *et al.*, 2001; Dulac *et al.*,

2007). Early and rational anti–epileptic treatment should be instituted in younger patients with a history of more than one seizure, cluster seizures or status epilepticus, despite the underlying cause. In fact, better seizure control and satisfactory long–term management are achievable where early, appropriate and aggressive anticonvulsant treatment is initiated. If and when an underlying cause can be identified and remedied (i.e. toxin exposure), anticonvulsant treatment can be slowly withdrawn over time; the suggestion is to reduce the dose by 25% every 3-4 weeks up to 5-6 months if the puppy or kitten has remained seizure free (Hoskins 2001). It is important to make the owner aware of the difficulty in attaining acceptable seizure control in some patients despite appropriate AED treatment.
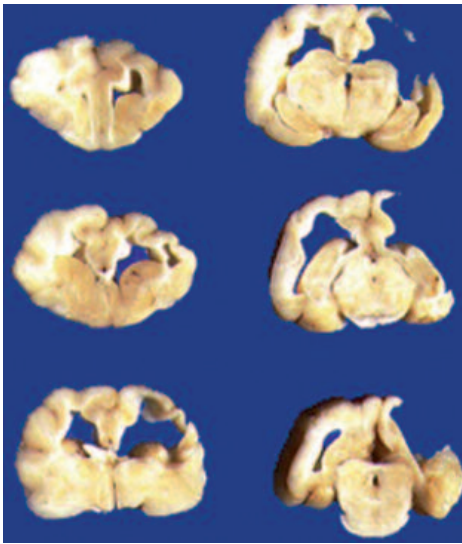
Fig. 5: *Porencephaly: 4-month-old, female, DSH cat with a 3-month history of progressive tetraparesis, seizures and visual deficits with normal pupillary light reflexes (PLR).*
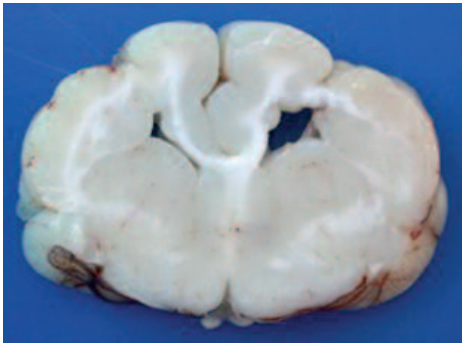*(Photograph courtesy of Carlo Cantile.)*

Fig. 6: *Lissencephaly: 2.5-month-old, male, domestic shorthaired male cat with a rapidly progressive seizure activity, which in a few days reached the frequency of one fit every 15 minutes. Administration of benzodiazepine was ineffective.*
(Photograph courtesy of Carlo Cantile.)

Fig. 7a: *Hydrocephalus: 5-month-old, male, Persian cat with a history of slow growth, depression, tetraparesis and seizures.*
(Photograph courtesy of Carlo Cantile.)

Fig. 7b: *7-month-old, male, crossbreed dog with a 2-month history of progressive disorientation, compulsive gait and seizures.*
(Photograph courtesy of Carlo Cantile.)

In cases with cluster seizure activity and status epilepticus, phenobarbitone and diazepam can be given *per rectum*, intravenously, intranasally, or via intraosseus and intraperitoneal routes; bromide can also be given *per os* or *per rectum* but has a much longer half life generally prohibiting its use in emergent situations.

HOW TO TREAT?

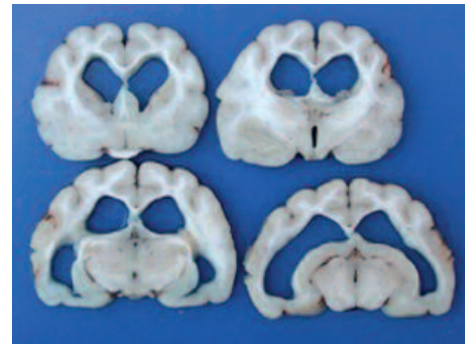Because there is a lack of clinical information regarding administration of AEDs in immature animals, the pharmacokinetics and drug disposition data have to be interpreted with caution before establishing an anti–epileptic protocol. Adult AED dosing protocols can be used as a guideline in younger animals. However, it has to be adjusted in view of the continuing growth, organ maturation and changing volume distribution to maintain the desired therapeutic serum level (Table 3). The owner should be made aware of the infrequent but potentially severe, life-threatening complications associated with each AED (Table 4).

ESTABLISHED AEDs
Bromide (Br)

Bromide (Br) is the oldest AED used in humans (Lancet, 1857); it has been recently reinstituted as AED in children with refractory epilepsy with no apparent long-term side effects (Takayanagi *et al.*, 2002). It can be used as first choice AED in dogs. As a monotherapy, bromide can be effective in approximately 80% dogs. Bromide is not protein

TABLE 3: Suggested AEDs in younger dogs and cats

AEDs oral dose	Puppies	Kittens
Bromide	30-40 mg/kg q 24h	~ 30 mg/kg q 24h
Phenobarbitone	0.5-2 mg/kg q 24h /q 12h	0.5-2 mg/kg q 24h
Diazepam	0.5-1 mg/kg q 8h	0.5-1 mg/kg q 8h
Gabapentin	10-20 mg/kg q 8h	10-20 mg/kg q 8h
Levetiracetam	10-30 mg /kg q 8h	10-30 mg/kg q 8h

TABLE 4: Common side effects of AEDs in younger dogs and cats

AEDs	Puppies	Kittens
Bromide	Polyuria, polydipsia, polyphagia, pelvic limbs ataxia, increased risk of pancreatitis	Possible life threatening respiratory complication
Phenobarbitone	Sedation, hepatotoxicity, bone marrow dyscrasia, cerebellar signs, polyuria, polydipsia, polyphagia, dermatitis, decreasing T4 level, behaviour changes, metabolic tolerance	Hepatotoxicity, necrotising dermatitis, behaviour changes, unpredictable blood level, metabolic tolerance
Diazepam	Sedation Functional tolerance	Acute liver failure Functional tolerance
Gabapentin	Sedation and lethargy at the beginning of treatment	Sedation and lethargy at the beginning of treatment
Levetiracetam	Not reported	No data available

Emergency loading dose

Bromide (*per os* or *per rectum*) = 600 mg/kg (divided over 3-6 days as necessary)

Phenobarbitone IV = BW x 0.8 x [desired serum concentration]

Dose adjustment for Br and Phenobarbitone

New dose = [desired concentration]/[actual concentration] X actual daily dose.

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bound and does not undergo hepatic metabolism. It is eliminated by the kidneys in a manner similar to chloride; consequently, diets with high chloride content can increase the bromide excretion and lower the serum Br concentration, increasing the risk of seizures.

Bromide may be an attractive AED in younger puppies with immature liver function. The reduced renal function allows shortening of the bromide half-life (~ 25 days in adult dogs), reaching steady state earlier and improving the seizure control (Bergman and Coates 2005). Typical side effects reported in adults are polydipsia, polyuria and polyphagia with the possible increased risk of pancreatitis. Bromide has been recently reported to have a very efficacious anticonvulsant activity in cats (Volk *et al.*, 2006), with the advantage of not being metabolised by the liver. However, Br has been associated with a high frequency of respiratory complications (~ 70%), similar to feline asthma syndrome. Respiratory complications can develop at any time during the treatment and may or may not be steroid responsive. Discontinuation of Br can resolve the respiratory signs in approximately 50% of the cases. However, the respiratory side effects have been severe in several cases, related to a fatal eosinophilic bronchopneumonia (Boothe and George, 2002). The owner should be made aware of this potentially severe, life threatening complication associated with Br therapy in cats.

Phenobarbitone (Pb)

Phenobarbitone is the most commonly used AED and has been proven to be as effective as bromide as an anticonvulsant. Phenobarbitone does not have significant protein binding (40-50%); 25% is eliminated unchanged by the kidney and it has a predominant hepatic metabolism. Phenobarbitone induced hepatotoxicity is well described in the literature and the risks are more elevated in immature dogs, due to the incomplete liver development and slow Pb elimination.

Phenobarbitone is a hepatic P450 enzyme inducer, consequently the half-life and efficacy decreases with long-term treatment. Phenobarbitone may also have a detrimental effect on the normal development of the nervous system with mental impairment and disturbance in the full brain growth documented in rats and children (Burgeois, 1995). Hoskins (2001) suggested the following protocols: phenobarbitone 0.5 mg/kg sid for animals younger than three months, 1 mg/kg bid for animals between three and six months of age, and 2 mg/kg bid for animals older than six months; bromide 40-80 mg/kg daily to increase if necessary to 120 mg/kg with serum level monitored at four and eight weeks after initiation and then every two months.

Diazepam

Parental diazepam is considered the first AED for emergency seizures treatment. However, its short half-life, increased hepatic enzyme induction, physical dependence and risk of acute and chronic liver failure, makes it less ideal as an AED for chronic seizure control.

NOVEL AEDS

Gabapentin and levetiracetam have not yet been fully evaluated in dogs and cats, However, due to the lack of hepatic enzyme induction and lack of significant reported side effects, they may be particularly promising AEDs in the younger animal.

Gabapentin

Gabapentin has minimal protein binding, and does not induce hepatic enzymes. Gabapentin is eliminated unchanged by the kidney and its

elimination does not change with chronic treatment. In dogs, as opposed to other species, it is approximately 30% metabolised by the liver.

Temporary lethargy and sedation are quite common. Gabapentin is a safe AED that has been proven efficacious in reducing seizure frequency and severity as an 'add-on' drug (Platt *et al.*, 2006) in refractory cases. It has been anecdotally used with success as monotherapy in cases of focal sensorimotor seizures.

Levetiracetam

Levetiracetam (LEV) is a new generation non–enzyme inducing AED. LEV has a high absorption rate, does not bind to plasma protein, is poorly metabolised, and lacks significant drug–drug interaction making it a favourable AED in younger animals. Initial sedation is the only minimal side effect reported in people. Multiple studies have recently shown that LEV exerts neuroprotective effects reducing the amount of inflammation and neuronal death that occurs with seizures (Hannon and Klitgaard 2001). Levetiracetam has been used as an adjunctive AED in refractory dogs with a few anecdotal reports suggesting its safety and efficacy (Volk et al 2007). The authors have successfully used levetiracetam in cats without significant side effects.

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KEY FACTS
- **A younger animal is more prone to seizures than an adult due to a more vulnerable developing brain.**
- **Seizure activity has to be considered an emergency and appropriate treatment established quickly.**
- **It is important to carefully rule out possible underlying causes that can lead to unsatisfactory treatment.**
- **The owner should be made aware of the potential adverse effects characteristics of each AED.**

These multiple choice questions are based on the above text. Answers appear on page 99.

1. **The most common cause of seizures in younger animals is not:**
    a. CNS neoplasia
    b. Idiopathic Epilepsy
    c. Congenital CNS malformation
    d. Metabolic disorder, toxic and intestinal parasitism
    e. Infectious and inflammatory CNS diseases

2. **Common side effects of long-term phenobarbitone treatment are:**
    a. Polydipsia
    b. Polydipsia/polyphagia
    c. Polydipsia/polyphagia–hepatopathy
    d. Hepatopathy
    e. Behaviour changes

3. **Bromide serum level is influenced by:**
    a. Diet
    b. Seizure frequency
    c. Liver disorders
    d. Kidney function
    e. None of the above