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CHAPTER 22

Seizures and Sleep Disorders

Fredrik Gruenenfelder

SEIZURES

Definition

I. A seizure is a nonspecifical, paroxysmal event or episode that may have a neurological or nonneurological etiology.
II. An epileptic seizure implies a neural cause.
III. An epileptic seizure is the clinical manifestation of involuntary alterations in behavior and locomotion caused by hypersynchronous, abnormal, neuronal activity in the cerebral cortex.
IV. Partial seizures arise from events in focal areas of the cerebral cortex.
    A. Paroxysmal alterations in motor function involve certain muscle groups, resulting in facial-muscle twitching, single-limb movements, or twisting of the head or neck.
    B. Paroxysmal alterations in vegetative or sensory functions cause abnormal behaviors, such as fly biting, excessive unmotivated vocalization, restlessness, unprovoked aggressiveness, drooling, or rapid running.
    C. No alteration in consciousness occurs during simple partial seizures, but consciousness is altered during complex partial seizures.
V. Generalized seizures originate from the cerebral hemispheres or thalamus and may begin with a focal event that progresses to involve the entire prosencephalon.
    A. Generalized seizures may be classified as tonic-clonic, clonic, atonic, or myoclonic.
    B. Autonomic disturbances, such as urination, defecation and hypersalivation, are common.
    C. Generalized seizures are often accompanied by alterations in consciousness.
VI. Unclassified seizures cannot be classified because of incomplete or inconsistent data.
VII. Certain events or phases may occur with seizures.
    A. The prodrome is the period before the onset of seizure activity.
        1. Prodromal signs include changes in behavior, such as anxiousness, increased attentiveness, or hiding.
        2. This phase can last for several days.
    B. The aura is the initial manifestation of a seizure.
        1. Signs include drooling, vomiting, pacing, or barking.
        2. The aura can last from seconds to minutes.
    C. Ictus is the actual seizure event and may include involuntary motor movements, abnormal muscle tone, abnormal sensation and behaviors; ictus usually lasts from seconds to minutes.
    D. The postictal phase is characterized by abnormal behavior, disorientation, weakness, blindness, and sensory or motor dysfunction that can last from minutes to 48 hours.
    E. The interictal period is the time between seizures, during which the animal is clinically and neurologically normal.
    F. Status epilepticus is a seizure lasting >5 minutes or repeated seizures without a return to consciousness between them (Thomas, 2003).
    G. Cluster seizures are defined as ≥2 seizures within 24 hours.
VIII. Epilepsy is defined as recurrent seizure activity caused by a chronic brain disorder (Berendt and Gram, 1999).
    A. Strictly defined, epilepsy does not imply an underlying cause of recurrent seizures.
    B. Epilepsy is commonly applied to situations in which an underlying cause is not defined and there may be a possible inheritance of the seizures.
        1. There is a familial predisposition for idiopathic epilepsy in certain breeds of dogs.
        2. In dogs, the age at onset is 1 to 5 years.
        3. Often the seizures are generalized, but they can be partial.
        4. Seizures occur spontaneously, often during rest or sleep.
        5. Seizure frequency initially is every 4 to 6 weeks.
        6. There is a tendency for frequency to increase if left untreated.
    C. Refractory epilepsy is frequent or severe seizure activity despite appropriate therapy.

Causes

I. Epilepsy can be classified based on the underlying etiology (Table 22-1).
II. Symptomatic epileptic seizures are caused by structural brain disorders.
III. Reactive epileptic seizures arise from disturbances in systemic metabolism or from toxicoses (no structural brain abnormalities).
IV. Cryptogenic epileptic seizures may occur from metabolic or structural brain disorders that are undetectable.

TABLE 22-1

Potential Causes of Seizures

CLASS OF DISORDERS	EXAMPLES
Degenerative diseases	Storage diseases: gangliosidosis, glucocerebrosidosis, glycoproteinosis, mucopolysaccharidosis glycogenosis, ceroid lipofuscinosis, leukodystrophy
	Diseases affecting intermediate metabolism
Anatomical anomalies	Hydrocephalus (primary, secondary), lissencephaly, hydranencephaly, porenecphaly
	Vascular malformations
Metabolic disturbances	Hepatic encephalopathy: portosystemic shunt, acquired liver disease
	Uremic encephalopathy
	Hypoglycemia: see Chapters 36 and 73
	Hypocalcemia: puerperal tetany, hypoparathyroidism
	Hypercalcemia, hypernatremia, hyponatremia, hyperlipoproteinemia
	Hypoxia, acid-base disturbances, polycythemia vera
Neoplasia	
Primary	Meningioma, meningiosarcoma, astrocytoma, glioblastoma multiforme
	Oligodendroglioma, oligoastrocytoma, gliomatosis cerebri
	Primitive neuroectodermal tumors, ependymoma, chorioid plexus papilloma
Secondary	Metastatic neoplasia, lymphoma
	Pituitary macroadenoma, hamartoma, suprasellar germ cell tumor
Inflammatory conditions	
Infections	
Bacterial	*Streptococcus* spp., *Staphylococcus* spp., *Escherichia coli, Pasteurella* spp., *Listeria monocytogenes*
Rickettsial	Rocky Mountain spotted fever, ehrlichiosis
Viral	Rabies, canine distemper virus, canine herpesvirus
	Feline infectious peritonitis, leukemia virus, immunodeficiency virus
Fungal	Cryptococcosis, blastomycosis, histoplasmosis, coccidiomycosis, phaeohyphomycosis
Protozoal	Neosporosis, toxoplasmosis
Parasitic	Dirofilariasis, toxascariasis, ancylostomiasis
Noninfectious causes	Granulomatous meningoencephalitis, necrotizing meningoencephalitis
	Necrotizing leukoencephalitis, eosinophilic meningoencephalitis
	Feline polioencephalomyelitis
Trauma	Head trauma: automobile crashes, high-rise building syndrome, bite wounds
Toxins	Organophosphates, carbamates, metaldehyde, pyrethrin (cats), ethylene glycol, bromethalin, lead
Vascular disorders	Hemorrhagic or ischemic infarction
	Feline ischemic encephalopathy from intracranial *Cuterebra* spp. larval migration

V. Idiopathic epileptic seizures have no recognized underlying metabolic or structural cause, and may be genetic in origin.

Pathophysiology

I. A seizure develops from transient, paroxysmal, uncontrolled, synchronized electrical discharge of neurons (Gandini et al., 2005).
II. The activity disperses to different areas of the brain over thalamocortical pathways, intrahemispheric association or commissural pathways (Podell, 2004).
III. The cause of the excessive electrical discharge may be an increased excitability of neurons (Gandini et al., 2005).
IV. A common mechanism may involve changes in equilibrium between the main inhibitory neurotransmitter (gamma aminobutyric acid [GABA]), and the main excitatory neurotransmitter (glutamate), with greater concentrations of glutamate (Fenner and Hass, 1989).
V. If the epileptic focus activates a critical number of areas, a generalized seizure occurs (March, 1998).
VI. Theoretically, the more new seizure foci that are recruited, the more difficult the seizures are to control medically (Podell, 2004).
VII. The end of the seizure is normally caused by active inhibition (Gandini et al., 2005).
VIII. Seizures can result in various secondary intracranial consequences.
  A. Accumulation of excitatory neurotransmitters (glutamate) can lead to neurotoxicity and neuronal cell death (Fujikawa, 2005).
  B. The disruption of neuronal function and integrity can lead to cerebral edema with increased intracranial

pressure and generalized, reduced perfusion of the brain (Podell, 2004).
C. Neurons have a much higher demand for energy during a seizure, which leads to anaerobic glycolysis, cerebral acidosis, and further neuronal dysfunction and death.

IX. Extracranial changes include hyperthermia, hypoventilation, hypoxia, and systemic hypertension.

Clinical Signs

I. Simple partial seizures
A. Motor movements in a single group of muscles: facial muscle or one leg twitching
B. No changes in consciousness

II. Complex partial seizures
A. Altered consciousness
B. Abnormal psychomotor function: fly biting, restlessness, barking, chasing of extremities

III. Generalized seizures
A. Impairment of consciousness
B. Excessive motor movements of the body and head (tonic/clonic movements)
1. In the tonic phase, the animal is in a rigid, hyperextended posture.
2. The clonic phase includes strong, jerky movements of the extremities, jaw, and neck muscles.
C. Autonomic disturbances: hypersalivation, urination, defecation

IV. Atonic, myoclonic, and absent seizures: difficult to recognize, poorly defined in animals

V. Other signs: pacing, transient loss of vision, disorientation, changes in personality

Diagnosis

I. Ultimate goal: determine the cause of the seizures

II. Important historical information
A. Vaccination status and travel history
B. Potential of trauma and exposure to toxins
C. Breed and familial history of seizures
D. Previous medical and surgical history
E. Onset and frequency of seizures
F. Duration of ictus
G. Duration and characteristics of the postictal phase

III. Physical examination
A. Detection of systemic illness that may result in reactive epilepsy
B. Identification of episodic nonneurological and neurological disorders easily confused with epileptic seizures

IV. Neurological examination
A. Perform a complete neurological examination to identify interictal deficits (see Chapter 21).
B. Asymmetrical, interictal deficits unrelated to postictal changes are suggestive of structural brain disease.

V. Minimal laboratory database
A. Complete blood count (CBC)
B. Serum biochemistry profile
C. Urinalysis

VI. Advanced clinicopathologic testing based on initial laboratory results
A. Liver function testing: bile acids, fasting serum ammonia, ammonia tolerance test
B. Simultaneous serum glucose and insulin levels in hypoglycemic animals
C. Serial blood glucose measurements in animals with suspected hypoglycemia
D. Endocrine assays: hyperadrenocorticism, hypoadrenocorticism, hypothyroidism
E. Toxicology testing: blood lead, acetylcholinesterase activity for organophosphate toxicities
F. Systemic blood pressure measurement

VII. Specific testing for intracranial disorders
A. Cerebrospinal fluid (CSF) analysis
B. Measurement of serum and CSF antibody or antigen titers
1. Feline enteric coronavirus/feline infectious peritonitis (FIP) virus
2. Canine distemper virus, *Neospora caninum*, *Toxoplasma gondii*
3. *Cryptococcus neoformans*, other fungal organisms

VIII. Imaging studies
A. Thoracic and abdominal radiography
B. Abdominal ultrasonography
C. Transcolonic portal scintigraphy
D. Magnetic resonance imaging (MRI) of the brain

IX. Establishing the type of seizures present
A. Idiopathic epilepsy (Table 22-2)
1. To classify the seizures as idiopathic epilepsy, the animal must have normal physical and neurological examinations and remain normal interictally.
2. Ultimately, the diagnosis of idiopathic epilepsy is made through the exclusion of other causes of epilepsy (i.e., symptomatic or reactive).
3. Clinicopathologic data are normal.
B. Symptomatic epilepsy
1. Hallmark findings are asymmetrical, neurological deficits or the persistence of any neurological deficit during the interictal period.
2. Age of onset is often <1 or >6 years.
3. Animals often have partial seizures, which may be generalized.
4. Clinicopathologic test results are usually normal.
5. Most cats have symptomatic or reactive epilepsy (Barnes et al., 2004; Quesnel et al., 1997).
C. Reactive epilepsy
1. Classic features are signs of systemic illness from metabolic disorders or toxicities (e.g., fever, lethargy, weight loss, anorexia, vomiting, diarrhea).
2. If present, interictal neurological deficits are symmetrical.
3. Seizures are often generalized.
4. Abnormalities are often found in clinicopathologic tests.
D. Cryptogenic epilepsy
1. Physical and neurological examination findings may be normal or abnormal.

TABLE 22-2

Clinical Features of Idiopathic Epilepsy

CLINICAL PARAMETER	DOGS	CATS
Cause	Genetic defects causing abnormalities in neuronal ion channels are suspected	Unknown
Incidence	50% to 60% of seizure disorders	10% to 20% of seizure disorders
Age of onset	1 to 5 years	Unknown
Affected breeds	Proven genetic factor: Keeshond Multiple factors (genetic and environmental): beagle, German shepherd dog, golden retriever, Belgian tervuren, Labrador retriever, Bernese mountain dog, boxer, Shetland sheep dog, viszla, Irish wolfhound High incidence: cocker spaniels, poodles, St. Bernard, Irish setter, miniature schnauzer, collie, wiredhaired fox terrier, dachshund, Greater Swiss mountain dog, Horaks laborhound, border collie	No breed predilection identified
Clinical signs	Sudden onset Seizures often generalized (tonic-clonic) Commonly occur at night or during rest/sleeping	Sudden onset Seizures often generalized: excessive activity, vocalizing, hypersalivation, defecation, urination

2. Clinicopathologic data may be normal or abnormal.
3. Despite lack of evidence or identification of an underlying etiology, cryptogenic epilepsy is often presumed in dogs <1 year or >5 years and in most cats with seizures.

X. Age relationship to causes in dogs (see Table 22-2)
   A. Age <1 year
      1. Dogs often have symptomatic or reactive epilepsy.
      2. Seizure activity often arises from congenital anomalies or inflammatory diseases of the central nervous system.
         a. Hydrocephalus: Chihuahua, Maltese, Yorkshire terrier, potentially any breed
         b. Canine distemper virus
         c. Noninfectious inflammatory diseases: necrotizing meningoencephalitis in the pug, necrotizing leukoencephalomyelitis in the Yorkshire terrier, Maltese, Chihuahua, and other small breeds
      3. Portosystemic shunts must always be ruled out in this age group.
   B. Age 1 to 5 years
      1. Most common cause: idiopathic epilepsy
      2. Later onset of seizure possible with congenital anomalies
   C. Age >5 years
      1. Intracranial neoplasia is a common cause.
      2. Cryptogenic epilepsy is suspected when an underlying etiology cannot be found.

XI. Age relationship to causes in cats
   A. Age <1 year
      1. Infectious inflammatory diseases: FIP, protozoal diseases
      2. Congenital anomalies of the brain
      3. Metabolic disorders, portosystemic shunts
   B. Age 1 to 7 years
      1. Infectious, inflammatory diseases
      2. Trauma
      3. Vascular insults: feline ischemic encephalopathy from *Cuterebra* spp. larval migration
      4. Neoplasia
   C. Age >7 years
      1. Neoplasia
      2. Metabolic diseases: renal encephalopathy
      3. Vascular insults: feline ischemic encephalopathy

Differential Diagnosis

I. Nonneurological disorders
   A. Syncope
   B. Stereotypy with abnormal behavior
   C. Strychnine intoxication

II. Neurological disorders
   A. Vestibular disorders
   B. Myasthenia gravis
   C. Narcolepsy, cataplexy
   D. Involuntary motor movements: myoclonus, generalized tremors, dyskinesia

Treatment

I. The goal of emergency treatment is to stop the seizure activity without causing any harm to the animal.
   A. Emergency treatment is required for isolated seizures lasting >3 minutes, seizures occurring hourly, three or more seizures within 12 hours, cluster seizures, and status epilepticus (Box 22-1).
   B. Initial emergency treatment involves controlling the seizure with short-acting anticonvulsants and initiating treatment with long-acting anticonvulsants.
      1. Benzodiazepines are used for initial treatment.

Box 22-1

Emergency Treatment of Status Epilepticus or Cluster Seizures in Dogs and Cats

1. Give diazepam 0.5 to 2 mg/kg IV or midazolam 0.07 to 0.22 mg/kg IV, IM and phenobarbital 2 mg/kg IV.
2. If seizures continue or recur within 2 hours, give an additional dose of diazepam or midazolam.
   a. A loading dosage of phenobarbital can also be given.
   b. The loading dosage of phenobarbital is 12 to 15 mg/kg IV divided into 2 to 4 mg/kg dosages every 1 to 2 hours over 24 hours until seizures are controlled or the animal is extremely sedated.
3. If seizures continue or recur within 2 hours, then consider propofol 4 to 8 mg/kg IV bolus and start constant rate infusion (CRI) of diazepam or midazolam at 0.5 mg/kg/hr IV.
4. If seizures do not stop, increase the CRI to 2 mg/kg/hr IV in 0.5 mg/kg/hr increments; at higher dosages animals can develop apnea.
5. If seizures stop, continue CRI of diazepam or midazolam for 4 to 6 hours, then gradually discontinue the CRI over 4 to 6 hours.
6. If seizures recur after stopping the CRI, restart a diazepam or midazolam CRI for another 6 hours and continue phenobarbital 2 mg/kg IV, IM, PO BID.
7. If seizures do not stop with repeated diazepam or midazolam, then give propofol 4 to 8 mg/kg IV and start a propofol CRI at 0.1 to 0.6 mg/kg/min IV for 4 to 6 hours.
8. If seizures stop, then gradually discontinue propofol CRI over 4 to 6 hours.
9. If seizures do not stop with diazepam, midazolam, or propofol, then consider pentobarbital 2 to 15 mg/kg IV over several minutes, then a pentobarbital CRI of 0.5 mg/kg/hr IV for 4 to 6 hours.
   Caution:
   a. Severe cardiopulmonary depression can occur.
   b. Endotracheal intubation may be necessary.
   c. Intensive monitoring is essential.
   d. Animal may be neurologically abnormal for up to 1 week after pentobarbital CRI.

   2. Diazepam is the drug of choice.
      a. It can be used for seizures or during the postictal phase.
      b. It may be administered IV, rectally, or intranasally.
   3. Midazolam can be used as an alternative.
C. In reactive epilepsy, treatment of the underlying etiology is undertaken.
D. With cryptogenic or idiopathic epileptic seizures, long-term anticonvulsive drugs are initiated simultaneously with benzodiazepine administration.
E. If seizures stop after emergency treatment, then continue with long-term anticonvulsants.

II. The goal of long-term treatment is to provide chronic control of seizure activity.
A. Theoretically, the goal is complete control of seizure activity (without side effects); however, this is rarely achieved.
B. A more realistic goal is to decrease the severity and frequency of seizures, and to prevent cluster seizures and status epilepticus while maintaining a good quality of life.
C. Successful long-term treatment requires dedication and understanding of realistic goals by the owners.
   1. Treatment is lifelong.
   2. Anticonvulsants must be given on a regular, daily basis.
   3. Seizure emergencies may occur despite appropriate treatment.
   4. Good knowledge of the potential side effects of anticonvulsants is imperative.
D. Reasons to initiate long-term anticonvulsive therapy include the following:
   1. After status epilepticus or cluster seizures
   2. After the occurrence of two or more isolated seizure events within a 6- to 8-week period
   3. After prolonged postictal periods
   4. In cases where an identifiable structural lesion is causing seizures
   5. Delayed onset of seizure activity after head trauma

III. Long-term anticonvulsants are initiated after emergency control of seizures (Table 22-3).
A. Phenobarbital is the anticonvulsant of choice and can be used in both dogs and cats.
   1. After emergency treatment, start phenobarbital at 2 to 5 mg/kg PO, IM, IV BID.
   2. If seizures persist despite initial emergency treatment, a loading dosage of phenobarbital can be administered (See Box 23-1).
   3. Alternatively, a loading dose can be calculated as follows:

$$\textbf{Loading dose (mg)} = \textbf{desired serum level (}\mu\textbf{g/mL)} \times \textbf{body weight (kg)} \times \textbf{0.8 L/kg} \; (\textbf{volume of distribution [Vd]})$$

   4. Animals are often heavily sedated for ≥24 hours when using the loading dose.
B. Potassium bromide (KBr) is a good second choice.
   1. It can be used in animals already receiving phenobarbital.
   2. In an emergency, KBr is administered as a loading dose because of its long half-life.
   3. Loading dosage is 400 to 600 mg/kg PO divided into six equal doses given over 1 to 5 days, depending on the severity of the seizures.
   4. Alternatively, a target steady state can be achieved based on the following formula:

$$\textbf{Target steady state concentration (Css)} \times \textbf{0.45 L/kg} \; (\textbf{[Vd]}) = \textbf{total dose administered}$$

   5. Target serum concentration for KBr as monotherapy is 1 to 3 mg/mL, and as adjunctive therapy with phenobarbital is 1 to 2 mg/mL.

TABLE 22-3

Anticonvulsant Drugs Available for Use in Dogs and Cats

DRUG	USE AND MECHANISM OF ACTION	PHARMACOLOGY	DOSAGES	SIDE EFFECTS AND CAUTIONS
Diazepam	Prolongs opening of GABA receptors; used for short-term control of seizures; drug of choice for emergency treatment of status epilepticus/cluster seizures; can be used for long-term management in cats	Metabolized in liver, excreted by kidneys (90%) and in feces (10%) Bioavailability: 80% $t_{1/2}$ (dogs): 3 hours $t_{1/2}$ (cats): 5 hours $t_{1/2}$ of active metabolite nordiazepam in cats = 21-hour maximum CNS concentration reached 1 minute after IV administration	*Dogs, cats:* 0.5-2 mg/kg IV, rectally CRI: 0.5-2 mg/kg/hr IV in 0.9% NaCl *Cats:* 0.5-2 mg/kg PO BID for long-term use	Sedation CRI can cause apnea Dogs develop tolerance Acute fulminant hepatic necrosis in cats (idiosyncratic) Used cautiously in animals with liver dysfunction
Midazolam	Prolongs opening of GABA receptors; used for short-term control of seizures; drug of choice for emergency treatment of seizures	Metabolized in liver, excreted by kidneys (>90%) and in feces (<10%) Bioavailability: 90% $t_{1/2}$ (dogs): 77 minutes	*Dogs:* 0.07-0.22 mg/kg IV, IM, intranasally, rectally CRI: 0.5-2 mg/kg/hr IV	Sedation CRI can cause apnea Used cautiously in animals with liver dysfunction No data for cats
Propofol	Effects GABA receptor ionophor complex; used for short-term control of seizures; drug of choice for emergency treatment of seizures not controlled with benzodiazepines; used for hepatopathy-induced seizures	Metabolized via extrahepatic routes; rapidly distributed to whole body; effects seen within 1 minute; anesthesia lasts 5 minutes after single bolus	*Dogs, cats:* 4-8 mg/kg IV to effect CRI: 0.1-0.6 mg/kg/min IV	Induces anesthesia (intubation necessary) Apnea and hypoxemia Myocardial depression
Phenobarbital	Increases neuronal response to GABA; prevents glutamate-induced postsypnatic decrease in neuronal calcium influx; used for generalize seizures	Metabolized in liver Bioavailability: 90% $t_{1/2}$ (dogs): 24-40 hours Tss: 10-14 days	*Dogs, cats:* 2-5 mg/kg PO BID	Transient: ataxia, lethargy, behavioral changes Persistent: PU/PD polyphagia, obesity, lethargy, splenomegaly, hepatomegaly, increased ALT and ALP, decreased serum thyroxine Severe side effects: hepatotoxicity, myelofibrosis, necrotizing superficial dermatitis
Potassium bromide	Hyperpolarization of neuronal membranes through chloride channels; used for generalized seizures	Excreted unmetabolized by kidneys Bioavailability: 60% $t_{1/2}$ (dogs): 25 days $t_{1/2}$ (cats): 10 days Tss (dogs): 90-120 days Tss (cats): 50 days	*Dogs, cats:* 30-60 mg/kg PO SID	Transient: ataxia, sedation, hyperactivity, vomiting Persistent: PU/PD Rare: aggression, dermatitis, pancreatitis Increased risk of asthma in cats; impaired renal function elevates blood levels; high salt diet increases bromide secretion

GABA, Gamma-aminobutyric acid; $t_{1/2}$, half-life time; *CNS,* central nervous system; *CRI,* constant rate infusion; *Tss,* time-to-steady rate; *PU/PD,* polyuria/polydipsia; *ALT,* alanine aminotransferase; *ALP,* alkaline phosphatase.

Continued

TABLE 22-3

Anticonvulsant Drugs Available for Use in Dogs and Cats—*cont'd*

Felbamate	Inhibition of NMDA receptors; potentiation of GABA receptors; used for partial seizures; added to phenobarbital and potassium bromide	Metabolized in liver (30%), excreted by kidneys (70%) Bioavailability: 85% $t_{1/2}$: 5-6 hours Tss: 24-30 hours	*Dogs:* 15-70 mg/kg PO BID-TID, increased in 15-mg/kg increments up to 70 mg/kg/day PO	Rare: nervousness, hyperexcitability, liver toxicity, bone marrow suppression No data for cats
Gabapentin	Mechanism of action not completely understood; may enhance effects of phenobarbital, diazepam, felbamate; added to phenobarbital and potassium bromide; also used for neurogenic pain management	Minimally metabolized in liver, excreted by kidneys Bioavailability: 80% $t_{1/2}$: 3-4 hours	*Dogs:* 25-60 mg/kg PO BID-TID	Rare: sedation Questionable efficacy in dogs, owing to short $t_{1/2}$ Can be used in cats, but no data available
Levetiracetam	Mechanism of action unknown; added to phenobarbital and potassium bromide; potentially a monodrug therapy; used for generalized seizures and hepatopathy-related seizures	Excreted unchanged or hydrolyzed by kidneys Bioavailability: ≈100% $t_{1/2}$: 4 hours Anticonvulsant effects last longer despite short $t_{1/2}$	*Dogs:* 25-60 mg/kg PO BID-TID	Rare: salivation, restlessness, vomiting, ataxia
Zonisamide	Blocks voltage-dependent sodium channels and t-type calcium channels; enhances dopaminergic and serotonergic neurotransmission; inhibits glutamate-induced excitation; added to phenobarbital and potassium bromide; used for generalized seizures	Metabolized in liver Bioavailability: 80% $t_{1/2}$: 15 hours Tss: 3 days	*Dogs:* 10 mg/kg PO BID	Rare: drowsiness, ataxia, gastrointestinal upset

NMDA, N-methyl-D-aspartic acid.

6. In animals already receiving KBr, the formula for a new oral dose for recurrent seizures is (Podell, 2004):

(Target Css) − actual Css × Vd L/kg = (target desired Css − actual Css) × 0.45 L/kg = mg/kg divided into 4 equal doses QID

7. KBr can be given PO or per rectum, but not IV.
8. Rectal administration can lead to severe diarrhea.
9. Maintenance dose is 30 to 40 mg/kg PO SID.
10. KBr is slowly increased to effect, to a maximum dose of 60 mg/kg/day PO.
11. KBr can be used safely in dogs.
12. KBr should be used with caution in cats, because it can result in tachypnea, dyspnea, and coughing (Boothe et al., 2002).
    a. Dosage is the same as in the dog.
    b. The half-life is 10 days, with steady-state serum concentrations being reached in 50 days (Boothe et al., 2002).
    c. KBr is avoided in cats because it may increase the risk of asthma.
    d. Discontinued if respiratory signs or radiographic changes develop.

C. Sodium bromide (NaBr; 3%) can be given IV.
1. It is dissolved in sterile water (0.375 mEq Br/mL + 1.3 mEq Na/mL)
2. An IV loading dose is calculated using the following formula:

Steady-state concentration (Css) × Vd = total dose administered by constant rate infusion (CRI) in a central vein

D. In cats, the pharmacokinetics of diazepam supports its use as a long-term anticonvulsant.
   1. Diazepam is given at 0.25 to 1 mg/kg PO BID.
   2. Side effects include sedation and polyphagia.
   3. In cats, oral administration can cause fulminant hepatic failure (idiosyncratic reaction), so it is only used as a last choice.
   4. Diazepam is not used as a long-term anticonvulsant in dogs.
      a. Dogs develop tolerance to long-term therapy.
      b. In dogs, the half-life is very short (3 hours).

E. Felbamate can be used in dogs if seizure control is insufficient with phenobarbital and KBr.
   1. Felbamate is given at 15 to 70 mg/kg PO BID to TID.
   2. Rare side effects include nervousness, hyperexcitability, liver toxicity, and bone marrow suppression.
   3. Felbamate may be useful for partial seizures (Ruehlmann et al., 2001).
   4. No data are available on its use in cats.

F. Gabapentin can be used in dogs if seizure control is insufficient with phenobarbital and KBr.
   1. Gabapentin is given at 25 to 60 mg/kg PO TID to QID.
   2. Short-term side effects include sedation; long-term side effects are unknown.
   3. No data are available on its use in cats, but administration of up to 30 mg/kg PO TID is anecdotally well tolerated in cats.

G. Levetiracetam can be used as a second-choice anticonvulsant in dogs if seizure control is insufficient with phenobarbital and KBr.
   1. Levetiracetam is given at 5 to 30 mg/kg PO BID to TID.
   2. It can be used in animals with hepatic dysfunction.
   3. Rare side effects include salivation, restlessness, vomiting, and ataxia.

H. Zonisamide can be used in dogs if seizure control is insufficient with phenobarbital and KBr.
   1. Zonisamide is given at 10 mg/kg PO BID (Dewey et al., 2004).
   2. Animals concurrently receiving phenobarbital may require higher dosages of zonisamide.
   3. Rare side effects include drowsiness, ataxia, and gastrointestinal irritation.
   4. Minimal side effects are seen at dosages up to 75 mg/kg/day.

IV. Recommendations for long-term management of seizures is as follows:
   A. Phenobarbital is the first-choice anticonvulsant because of its faster onset of action, shorter half-life, and more predictable anticonvulsant effects.
      1. Animals are initially started on phenobarbital at 2 mg/kg PO BID.
      2. If seizure control is poor after reaching the steady state, the dosage of phenobarbital is gradually increased to approximately 5 mg/kg PO BID.
   B. If seizure control remains poor or severe side effects occur, KBr therapy is initiated at 30 mg/kg PO SID.
   C. If seizure control remains poor despite the addition of KBr, the dosage of KBr is gradually increased to a maximum of 60 mg/kg PO SID.
   D. If the animal does not tolerate phenobarbital well, monotherapy with KBr is initiated.
   E. In animals experiencing side effects or in those that are seizure-free for >1 year, the dosage of anticonvulsants can be gradually decreased.
   F. Second-choice anticonvulsants are typically used if seizures cannot be controlled with a combination of phenobarbital and KBr, or if side effects are intolerable.

Monitoring of Animal

I. Animals undergoing emergency treatment for seizures require intensive supportive care and monitoring.
   A. IV fluid therapy is administered for maintenance needs and any ongoing losses.
   B. Fluid input and output are closely monitored to maintain hydration.
   C. Supplementation with thiamine 25 to 50 mg IM, IV may be helpful, as thiamine is essential for glucose metabolism in the brain.
   D. Periodic monitoring of packed cell volume, total solids, blood glucose, serum calcium, and blood urea nitrogen is done.
   E. Monitor body temperature to avoid hyperthermia or hypothermia.
   F. Recumbent animals are turned every 4 to 6 hours.
   G. Animals receiving anticonvulsants by CRI are monitored as follows:
      1. Heart rate, respiratory rate, and temperature are measured every hour.
      2. Blood pressure and oxygenation via pulse oximetry or arterial blood gas analysis are monitored every 4 hours
      3. Monitor for slowing of respiratory rate, hypoventilation, and apnea, which may necessitate mechanical ventilation.
      4. Tracheal intubation may be necessary.
      5. Supplemental oxygen may be needed for hypoxemia.
      6. Change endotracheal tubes every 6 hours.

II. Owners may be taught to provide emergency treatment at home for seizures lasting >5 minutes, status epilepticus, cluster seizures, or postictal phases >2 hours.
   A. Diazepam can be administered rectally in dogs at 1 to 2 mg/kg (Podell, 1995).
      1. Use parenteral diazepam solution or commercially available rectal compounds.
      2. Diazepam is absorbed quickly across the rectal mucosa, reaching peak plasma concentration within 15 minutes.
      3. The first-pass effect is avoided with rectal application.
      4. Effects of rectal diazepam last for about 1 hour.
   B. Diazepam can be administered rectally in cats at 0.5 to 1 mg/kg.
      1. Pharmacokinetics are unknown, but may be similar to the dog.

2. Effects are seen within 10 to 15 minutes.
3. Diazepam may be less effective if the cat is also receiving long-term treatment with diazepam.

III. Monitoring of long-term anticonvulsant therapy is done through evaluations of clinical signs, seizure frequency, and measurement of serum drug levels.
   A. If an anticonvulsant is used within the recommended dosage range and the seizures are under control, serum levels may not be needed.
   B. Avoid under- or overdosing of drugs.
   C. Note that an animal can develop severe side effects despite having normal to low serum levels.
   D. Serum monitoring is recommended if seizure control is poor, the animal shows signs of toxicity, or severe side effects occur after initial adaptation to the drug.
   E. Monitoring serum levels allows for individualized treatment and minimizes the potential for side effects.
   F. Phenobarbital or KBr dosages can be incrementally increased when seizure control is poor or decreased to reduce side effects or toxicity.

IV. Dose adjustment of phenobarbital is initially based on the degree of seizure control.
   A. If the high end of the dosage range is needed to control seizures, serum phenobarbital levels are measured to prevent toxicity.
      1. Levels can be checked at any time during the day after steady state has been reached.
      2. Avoid serum separator tubes, because silicon binds phenobarbital and results in artificially low serum levels.
      3. Therapeutic serum phenobarbital levels (dependent on laboratory) are as follows:
         a. Dogs: 20 to 40 μg/mL
         b. Cats: 10 to 30 μg/mL
   B. Side effects of phenobarbital are listed in Table 22-3.
   C. A CBC, biochemistry profile, and urinalysis are performed every 6 months.
   D. When using serum phenobarbital levels to change dosages, a formula can be used:

(Desired concentration ÷ actual concentration) × total mg/day = new total mg dose phenobarbital/day

V. Serum KBr levels are evaluated if seizure control is poor or if toxicity is suspected.
   A. Serum levels can be checked at any time during the day after steady state has been reached.
   B. If used as monotherapy, therapeutic levels in dogs are 2 to 3 mg/mL.
   C. If used in combination with phenobarbital, therapeutic levels in dogs are 1 to 2 mg/mL (March et al., 2002).
   D. KBr can be adjusted using the following formula (Podell, 2004):

(Target Css – actual Css) × (0.02 × clearance/bioavailability) = new maintenance dose (added mg/kg/day)

   E. Side effects are listed in Table 22-3.
   F. Monitor CBC, serum biochemical profile, and urinalysis every 6 months.

VI. Optimizing seizure control involves several steps.
   A. It is imperative that an underlying cause be established, if possible.
      1. The earlier proper treatment is initiated, the better the chance for optimal control.
      2. In idiopathic epilepsy, anticonvulsive treatment is lifelong.
   B. Underdosing anticonvulsant drugs can lead to poor seizure control.
   C. Client education regarding realistic goals of seizure control and anticonvulsant side effects is required.
   D. If the animal is seizure free for >1 year, a slow, incremental reduction of the drugs may be tried over 6 months.

SLEEP DISORDERS

Definition

I. Narcolepsy is an abnormality in the sleep–wake cycle that manifests as excessive sleepiness and uncontrollable episodes of sleep.
II. Cataplexy is a short episode of complete loss of muscle tone, usually provoked by excitement and emotion.
   A. Loss of muscle tone is caused by central-mediated inhibition of α-motor neurons.
   B. Episodes are reversible.
   C. Consciousness is not altered in pure cataplexy.
   D. Cataplexy occurs often together with narcolepsy.

Causes

I. In dogs, narcolepsy can be caused by an inherited, autosomal, recessive defect of the hypocretin-receptor-2 gene (Lin et al., 1999).
II. Affected breeds include the Doberman pinscher, Labrador retriever, dachshund, and poodle.
III. Narcolepsy can also result from a decreased level of hypocretin-1 protein.
   A. Although the cause remains unknown, an autoimmune process is suspected.
   B. Affected breeds include the Airedale terrier, Afghan hound, Irish setter, malamute, St. Bernard, rottweiler, English springer spaniel, Weimaraner, Welsh corgi, and giant schnauzer.
IV. Inflammatory, neoplastic, or vascular lesions involving the hypothalamus may also be causes.
V. Narcolepsy is rare in cats.

Pathophysiology

I. Hypocretin-1 protein and the hypocretin-receptor-2 play important roles in the sleep–wake cycle and in control of α-motor neurons in the spinal cord (Yamuy et al., 2004).
II. Neurons containing hypocretin-1 are located predominantly in the posterior hypothalamus.
III. Fibers from these neurons are distributed to the locus coeruleus, nucleus raphe, and cerebral cortex.
   A. Binding of hypocretin-1 to the hypocretin-receptor-2 has a rousing effect and increases motor activity.

B. Deficiency in the numbers of functional hypocretin-receptor-2 leads to decreased effects of hypocretin-1 protein.
C. Similarly, a deficiency in the amount of hypocretin-1 protein also leads to diminished effects.
D. The result is an abnormal sleep–wake cycle regulation, leading to excessive sleepiness and episodes of sleep.
E. A loss of hypothalamic hypocretinergic control of α-motor neuron leads to loss of muscle tone and cataplexy.

Clinical Signs

I. Affected animals are typically <6 months; however, onset can occur in young adult animals.
II. Episodes are often provoked by excitement (e.g., feeding, drinking, playing).
III. Episodes consist of immediate onset of active sleep with rapid eye movement followed by a sudden return to a normal awake state (narcolepsy).
IV. Generalized muscle atonia (cataplexy) may also occur.
V. Affected animals often have prolonged sleep periods, as well as marked drowsiness during the day.
VI. Onset and termination of the episodes are abrupt.
VII. Duration of episodes ranges from seconds to 30 minutes.
VIII. External stimuli can often interrupt the episode.

Diagnosis

I. Presumptive diagnosis is made by observing an episode.
II. Breed, history, and clinical signs are supportive.
III. Episodes can be induced.
  A. Food-elicited cataplexy test (FECT)
    1. Line up about 10 small treats, 30 cm apart.
    2. Observe the animal for loss of muscle tone or sleep episodes.
    3. Record the time it takes for the animal to eat all the treats.
    4. A normal dog can eat the food within 1 minute without an episode occurring.
    5. A positive test result involves the following observations:
      a. The animal has two or more episodes and takes >2 minutes to eat all the treats.
      b. The animal falls completely asleep.
      c. The dog drops to the floor, but the head stays in a normal position.
  B. Pharmacological tests
    1. Yohimbine response test
      a. Yohimbine is administered at 50 μg/kg IV.
      b. A positive response is a 75% reduction in number or duration of episodes.
      c. The effect of yohimbine lasts 30 to 240 minutes.
    2. Anticholinergic drugs
      a. They can increase the duration and/or frequency of the episodes.
      b. The FECT is performed after administration of atropine 0.1 mg/kg IV or physostigmine 0.025 to 0.1 mg/kg IV.
      c. Affected animals have increased frequency and/or duration of episodes.
    3. Imipramine challenge
      a. Imipramine is administered at 0.5 mg/kg IV.
      b. A positive response consists of a decrease in episodes, but is not specific for narcolepsy and/or cataplexy.
IV. CSF analysis may be helpful (Mignot et al., 2002).
  A. Hypocretin-1 concentration can be measured in CSF by the Center for Narcolepsy, Department of Psychiatry, Stanford University School of Medicine.
    1. A level <100 pg/mL is consistent with narcolepsy from hypocretin-1 deficiency.
    2. A level of 101 to 200 pg/mL is suspicious for narcolepsy from hypocretin-1 insufficiency.
    3. Levels of 200 to 350 pg/mL are normal (Ripley et al., 2001).
  B. CSF analysis can help establish an underlying cause or rule out other disorders.
V. Genetic analysis also can be performed at Stanford University School of Medicine.

Differential Diagnosis

I. Myasthenia gravis
II. Syncope
III. Seizures
IV. Metabolic disturbances: hypoglycemia, hypocalcemia, hypokalemia, hyperkalemia, hypoadrenocorticism

Treatment

I. Cataplexy is usually treated with tricyclic antidepressants or selective serotonin reuptake inhibitors (Thomas, 2003).
  A. Imipramine 0.5 to 1 mg/kg PO BID to TID
  B. Desipramine 3 mg/kg PO BID
  C. Amitriptyline 1 to 2 mg/kg PO BID
  D. Protriptyline 5 to 10 mg/kg PO SID
II. Excessive sleepiness and sleep attacks are treated with sympathomimetics or monoamine oxidase-B inhibitors.
  A. Methylphenidate 0.25 mg/kg PO BID to TID
  B. Dextroamphetamine 5 to 10 mg PO BID to TID
  C. Selegiline 1 mg/kg PO SID (Thomas, 2003)
III. If an underlying etiology is identified, treatment is directed at the cause.
IV. Side effects of medical therapy include the following:
  A. Amphetamines can cause behavioral changes.
  B. If a combination of amphetamine and imipramine is used, severe catecholamine accumulation may occur from increased release and inhibition of reuptake.

Monitoring of Animal

I. Prognosis for a good quality of life is moderate to good.
II. Some animals improve with age.
III. Lifelong therapy is often required.
IV. Lifestyle changes that decrease triggering events help to improve the quality of life.

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