Anticonvulsant Therapy and the Role of Therapeutic Drug Monitoring (Part 1)

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INTRODUCTION

Successful control of seizures with anticonvulsant drugs reflects a balance in achieving seizure control while minimizing undesirable drug side effects. Variability in the disposition of anticonvulsants and interactions among them and other drugs are important confounders of successful therapy. This chapter reviews selected anticonvulsants, focusing on the drugs that are most likely to control seizures in small animals. The proper use of anticonvulsants is discussed, with an emphasis on the differences in individual drug disposition, detection of these differences, and rational approaches to responding to these differences by dose modification. The primary topic of discussion is treatment of generalized, tonic-clonic seizures, the most common type afflicting small animals. Opinions regarding anticonvulsant therapy vary among clinicians. Most of the comments and recommendations offered in this discussion reflect personal observations in a therapeutic drug monitoring service and completed as well as ongoing clinical trials that focus on the use of anticonvulsants either alone or in combination with phenobarbital.

It is important to approach epilepsy as a clinical manifestation of an underlying disease. Thus, therapy is more likely to be effective if the underlying disease is treated. Such causes should be identified and appropriately treated, and if possible, before chronic anticonvulsant therapy is instituted. Undesirable side effects are often the limiting factor in the use of anticonvulsant drugs, and not all seizures necessarily need to be treated.

Eradication of seizures may not be a reasonable expectation; for some patients, success is an acceptable reduction of seizures. Because therapy is life-long, the risk of adversity is increased: as long as the patient is on the drugs, toxicity or drug interactions can complicate success. Success is most like if the underlying cause is corrected. Among the considerations is whether or not to start antiepileptic therapy.

Although this is patient dependent, acceptable criteria for beginning therapy are seizures that are greater than 3 minutes in duration (longer may increase the risk of cerebral hypoxia, hyperthermia and cluster seizures), cluster seizures (variably defined, but

generally 3 or more seizures that occur without regaining consciousness), more than one seizure a month, or a worsening seizure pattern indicative of worsening disease.

Mechanisms of action: A seizure occurs after inappropriate firing of a neuron. As with other cells, the resting membrane potential is negative, being maintained by intra and extracellular concentrations of negative ions (chloride) and positive ions (sodium, potassium calcium). The proper ratio is maintained by the energy dependent ATPase pump. The sum effect of these ions reflects, in turn, the sum influence of neurotransmitters at the presynaptic terminal. Most neurotransmitters are excitatory, with the major being acetylcholine, glutamate (which interfaces with N-methylaspartate receptors), and catecholamines (epinephrine, norepi and dopamine). The most important inhibitory neurotransmitter is GABA aminobutyric acid, or GABA. The GABA receptor has agonistic sites for binding by GABA, as well as endogenous benzodiazepines and barbiturates. Binding by agonists results in the opening of a channel through which chloride ions influx into the cell result in its hyperpolarization. Underlying mechanisms that can lead to neuronal disruption and seizures include altered function of the cell membrane such that ion fluxes are not maintained. Examples include hypoglycemia and/or hypoxia (loss of energy), altered membrane permeability such as might accompany hypoxia, inflammation or cancer, and altered electrolytes in the plasma (e.g., calcium, potassium). Neurotransmitters might be altered: decreased inhibitory or increased stimulatory signals may reflect genetic diseases or metabolic diseases such as renal or liver disease characterized by accumulation of waste toxins that might mimic or influence neurotransmitters. While it is appealing to target seizure control by correcting this abnormalities, the actual cause is often not known. An exception might be tumor or inflammation. Simple inappropriate firing of a neuron, or initiation, is not enough to cause a seizure. The neuron must recruit surrounding neurons which must then be synchronized to finally propagate the signal. The further the signal is propagated, the greater the clinical manifestation of the seizure. Focal seizures are limited in spread whereas tonic-clonic seizures are widely propagated.

Most anticonvulsant drugs have more than one mechanism of action. Drugs can interface with gamma amino butyric acid (GABA) receptors. This opens a post synaptic gate that allows chloride ions to flow into the neuron, hyperpolarizing it. Drugs which target GABA receptors include barbiturates and benzodiazepines which have a specific site on the receptor (suggesting the existence of endogenous compounds). Gabapentin appears to somehow influence GABA. Other drugs influence neuronal ion fluxes, particularly decreasing sodium and/or calcium (e.g., phenobarbital and zonisamide, and possibly bromide). Levetiracetam interferes with the release of synaptic vesicles. Not shown is the potential for some drugs (e.g., phenobarbital) to decrease glutamate. As a reminder, drugs which are able to penetrate the CNS general cause changes in CNS physiology. Adaptation

to the drug might be manifested as tolerance, meaning a higher concentration is necessary to maintain control. Physical dependence is common: rapid withdrawal may put the patient at risk for severe seizures, including status epilepticus. As such, drugs with short half-lives should be tapered rather than abruptly discontinued.

Disposition: The disposition of antiepileptics markedly influences therapeutic success and safety. Most orally administered drugs are characterized by good bioavailability. However, human products, particularly slow release, are designed for humans and may not extrapolate well to animals. Antiepileptics generally must be lipid soluble in able to penetrate the blood brain barrier. As such, they are generally characterized by a volume of distribution that is at least 0.6 L/kg. This generally results in a longer half-life for the more lipid soluble drugs. Those drugs that are lipid soluble will undergo hepatic metabolism to avoid passive reabsorption in the kidney. Each step of metabolism increases water solubility and thus renal excretion. Hepatic metabolism has other implications for safety and efficacy. Hepatic metabolism increases the risk of liver disease since metabolites generally are oxygen radicals. Drugs which are metabolized by cytochrome P450 (CYP 450) are subject to and may be the cause of drug interactions involving these enzymes, which means there is a risk of drug interactions involving drug metabolizing enzymes. The impact of metabolism can be inactivation, but also may result in the formation of toxic metabolites (such as phenobarbital). Some drugs are metabolized to active metabolites (e.g., diazepam) which prolongs their half-life. Note that some drugs are metabolized by non-hepatic routes (e.g., levetiracetam).

Combination therapy. Ideally, monotherapy is preferred to combination therapy; monotherapy should not be considered to have failed until either undesirable side effects emerge, or drug concentrations at the maximum acceptable range have been surpassed. Monitoring is indicated to confirm determine therapeutic failure, potential toxicity and to establish baseline concentrations such that proactive changes in anticonvulsants can be recognized. Monitoring at Auburn University can be found at **www.vetmed.auburn.edu/veterinarians/clinical-labs**. Use of combination therapy appears to be popular in veterinary medicine, based on therapeutic drug monitoring information in the author's laboratory. Although combination therapy is a reasonable approach for control of seizures in patients that fail to reasonably respond to first choice anticonvulsants (e.g., plasma drug concentrations approach or enter the high end of the therapeutic range, or unacceptable side effects emerge), many of these patients are on two or more, drugs each of which is in the sub to low therapeutic range, The American Epilepsy Society notes that most humans can be controlled with single drug therapy and that higher concentrations of a single drug is preferred to lower concentrations of multiple drugs. Single therapy should be considered prudent for several reasons. The most obvious is avoidance of side effects (the combined side effects of a drug might, like efficacy, be worse than either

drug by itself), fewer drug interactions, better owner compliance and reduced cost due to the need for more than one prescription and monitoring more than one drug. Other reasons to limit combination therapy to patients with proven need are likely to be less obvious. However, no drug therapy is likely to be innocuous. Drugs that affect the CNS may be problematic because of the sophisticated mechanisms which exist to minimize the effects of CNS drugs. This includes efflux proteins, receptor down regulation or desensitization. In the author's opinion, because the CNS does not *want* drugs in the CNS, an attempt should be made to respect the body's attempt to limit exposure of the brain to drugs. Accordingly, the author recommends that single drug therapy be targeted and combination therapy be instituted only in patients that have failed initial therapy.

Discontinuing therapy. Whether or not anticonvulsant therapy facilitates remission of spontaneous seizures is not clear, although a tendency for contemporary anticonvulsant therapy to be associated with epileptic cure has been described in humans. In human medicine, AED drugs can be withdrawn in 60% of patients that remain seizure free for 2 to 4 years. A similar statistic is not available in veterinary medicine. The likelihood of success can be somewhat correlated with the underlying cause or type of seizure, with the best being the patient with idiopathic generalized epilepsy in non-juveniles, a normal neurologic exam, and the absence of a structural brain lesions. We have recommended that therapy might be discontinued in those patients whose drug concentrations are below the recommended therapeutic range. Should the decision be made to discontinue therapy, we recommend that concentrations first be monitored (to provide a target to which concentrations can be returned if the patient seizures) and then the antiepileptic drug be slowly discontinued over several months (e.g., 25% each month). Note that with each decrease, the response should be assessed after the drug has reached steady-state plus one seizure interval (i.e., assure, as much as possible) that the patient is challenged by a seizure before the next decrease is implemented).

Levetiracetam is a single (S)-enantiomer acetamide derivative AED drug. Its mechanism of action is novel and does not appear to involve any known neurotransmitter, ion channel protein or receptors. Levetiracetam was most useful experimentally in blocking seizures caused by pilocarpine and kainic acid, and in the kindling model of rats, both models for complex partial seizures with secondary generalization. Food does not impair the extent, but does impair the rate, of oral absorption. In humans, close to 70% of the drug is renally excreted; hepatic metabolism of the remainder reflect acetamide hydrolysis, which is not CYP 450 dependent. Levetiracetam is metabolized by plasma B- esterases which will continue once blood is drawn. As such, serum rather than plasma or whole blood is the desired test tissue of choice. The elimination half-life in humans is approximately 7 hrs. Drug

interactions appear to be minimal; competition for renal tubular secretory proteins may occur.

The disposition of levetiracetam has been described in mongrel dogs (n=6). Following IV administration of 20 mg/kg yielded, a maximum concentration of approximately 44 mcg/ml, a VD of 0.45±0.13 l/kg, a clearance of 1.5 ml/min/kg, and elimination half-life of 3.6±0.8 hr and MRT of 5±1 hr. Patterson studied levetiracetam after IV, IM and PO (19.5–22.6 mg/kg) administration in Hound dogs (n=6). Peak drug concentrations were 37±5, 30.3±3 and 30±4 mcg/ml after IV (Co), IM and PO administration, respectively. The volume of distribution (beta) was 0.55 L/kg and clearance was 55 ml/min (not standardized to kg). Elimination half-life was 3±0.3 hr. Bioavailability after IM and oral administration were 113+13% and 100+7%, respectively. No pain was detected with intentional perivascular injection.

In dogs, 1200 mg/kg IV or 2000 mg/kg PO were not lethal but were associated with salivation, vomiting, tachycardia and restlessness. Long-term administration (≥6 months) in some species was associated with enzyme induction (centrilobular hypertrophy) at 50 mg/kg/day. In the dog, 1200 mg/kg/day for 13 and 52 weeks resulted in transient restlessness and tremor, and centrally mediated salivation and vomiting. Liver weight increased, although histopathological changes did not appear in the liver.

The disposition of levetiracetam has been described in cats (n=10) receiving 20 mg/kg either IV or PO as a single dose. Cats tolerated dosing well, with no significant adverse effects noted. However transient mild to moderate degree of hypersalivation occurred with oral dosing. Clearance (ml/kg/min) was 2.0 ml/kg/min (range 1.5–3.4 ml/kg/min) and Vd_{ss} was 0.52 L/kg (range, 0.33–0.64 L/kg). After oral dosing, in 7 of 10 cats, therapeutic plasma concentrations were achieved within 10 minutes and remained within the therapeutic range for at least 9 hours. Median peak concentration (C_{max}) was 25.54 µg/mL (range, 13.22–37.11 µg/mL), T_{max} was 1.67 hours (range 0.33–4.0 hours), $T_{1/2}$ was 2.95 hours (range 1.86–4.63 hours) and MRT was 5.65 hours (range, 4.23–7.86). Mean oral bioavailability was 100%. Response to levetiracetam of dogs (n=14) with refractory epilepsy was described prospectively. Levetiracetam was administered at 10 mg/kg orally every 8 hr; the dose was increased to 20 mg/kg tid if seizures did not decline by at least 50%. At two months, 8/10 dogs responded with seizure number reduced by 73% and number of days/month reduced by 67%. At 6 months, 6/11 dogs remained classified as responders. However, with long-term follow-up, only 3 animals remained responders, suggesting that efficacy of levetiracetam declined. Drug concentrations were not measured; as such, the cause of therapeutic failure due to tolerance or worsening disease was not discriminated from declining drug concentrations. The use of levetiracetam in cats has been reported. Four cats with seizure disorders that were poorly controlled with PB alone were treated with oral LEV as an add-on

drug at a dose regimen of 20 mg/kg body weight, q 8 h. LEV serum concentrations were within the reported therapeutic range for people (5–45 µg/ml) for all samples in all cats. The slow release levetiracetam product has been studied in dogs at 30 mg/kg orally. Pharmacokinetic parameters for oral extended release dosing in fasted and fed animals, respectively, were: C_{max}=27±6 and 31±7 mcg/ml, T_{max}=204±46 and 394±90 minutes, $t_{½}$=4.4±2.1 and 4.2±1.1 hours, MRT=9.8±2.0 and 10.±1.8 hours, MAT=4.7±0.9 and 5.6±1.7 hours, and F=1.04±0.12 and1.26±0.20%. Serum levetiracetam remained above the minimum therapeutic range (humans: 5 mcg/ml) for approximately 20 hours in both fasted and fed animals.

It is important note that the capsule **cannot** be broken and as such, the smallest size dog that might be treated with the human preparations is 15 kg. However, the drug is safe enough that smaller dogs might be treated. Recent studies using the extended release product have demonstrated safety in cats as well.

Zonisamide: Developed in Japan, zonisamide (zonisamide), 3-sulfamoylmethyl-1,2-benzisoxazole, is a synthetic sulfonamide-based anticonvulsant approved for use in the USA in 1998 for treatment of seizures related to human epilepsy. The efficacy of zonisamide for treatment of human epilepsy is similar to phenobarbital and superior to other classic drugs including valproic acid and phenytoin. Its mechanism is not clear, but it appears to inhibit neuronal voltage-dependent sodium and T-type calcium channels. It also modulates the dopaminergic system and accelerates the release of γ-amino butyric acid (GABA) from the hippocampus. An additional potential advantage of zonisamide is free radical scavenging which protects against the destructive nature of radicals, especially in neuronal membranes. Finally, zonisamide blocks the propagation of seizures from cortex to subcortical areas of the brain. Its AED efficacy, has been described similar to phenytoin or valproic acid, thus minimally impacting normal neuronal activity. These multiple mechanisms of action may translate to improved efficacy compared to other anticonvulsant drugs. The clinical pharmacology of zonisamide has been investigated in humans with similar characteristics in dogs. Disposition is complicated. Oral absorption tends to be rapid, complete and minimally impaired by food. After 12 hours of dosing, zonisamide concentrations in the brain are two fold that in plasma. The extent of protein binding does not limit the rapid movement into the brain. Binding of zonisamide to erythrocytes (RBC) and plasma proteins contributes to complex kinetics. Erythrocyte concentrations in whole blood tend to be twice as high as plasma and serum in humans, and is characterized by binding that is both saturable and non-saturable; the saturable portion may reflect binding to carbonic anhydrase in epileptic patients. Accumulation of drug in RBC is reversible, and the complex relationship between zonisamide and RBC may make therapeutic drug monitoring of plasma or serum advantageous. Metabolism of zonisamide

involves both phase I and phase II hepatic metabolism with cytochrome P450 3A4 being the major isozyme and a glucuronidated compound the major metabolite. Enzymes CYP3A4, CYP3A5, CYP2C19 contribute to metabolism in humans. Renal elimination and recovery of zonisamide indicates parent drug recovery of 35%. Using radio labeled (carbon) zonisamide administered to dogs, 83% of the drug was excreted in 72 hour urine as the either the parent compound or metabolites. The terminal half-life of zonisamide in the dog was 15 to 42 hours; the longer elimination half-life allows a convenient dosing interval while minimizing dramatic fluctuations in zonisamide concentrations that might cause recurrence of seizures. Recommended therapeutic concentrations are initially 10 to 40 mcg/ml; however, monitoring should be based on patient need. Non-linear pharmacokinetics have been reported in some human patients, particularly with chronic dosing, resulting in disproportionate, and thus unexpected, increases in drug concentrations compared to changes in dose. In dogs undergoing toxicity studies, plasma concentrations, never reached steady state over the course of thirteen weeks of dosing at 75 mg/kg, compared to proportional steady state concentrations by week 13 at 10 to 30 mg/ kg. However, in the author's laboratory, many dogs reveal disproportionate increases in zonisamide for dose increases, particularly when concentrations already are at high (>50 mcg/ml) levels. This may also reflect, however, discontinuation of phenobarbital in some of the patients but it also reflect saturation of drug metabolizing enzymes since zonisamide is acetylated and dogs are deficient acetylators.

Clinical pharmacokinetics of zonisamide have been described in normal dogs (n=8); 4 male and 4 female) ranging from 3 to 4 years of age using a randomized crossover design following single intravenous (IV) and oral administration, 6.85 and 10.25 mg/kg, respectively. The half-life at 8 weeks was 23±6 hrs. Plasma drug concentrations varied by 17.2% between 12 hour dosing intervals, suggesting a 12 hr dosing interval is appropriate. Differences in clinical pathology data occurred at the end of the 8 week study period, although all results remained within normal limits. Serum alkaline phosphatase and calcium increased above baseline, whereas total serum protein and albumin both decreased below baseline.

Zonisamide pharmacokinetics have been described in cats (n=5) following a single 10 mg/kg dose (Table 1).[216] Safety and adverse reactions were studied during chronic (9 weeks) dosing at 20 mg/kg once daily. Zonisamide was not well tolerated at this dose; 50% of cats exhibited vomiting, diarrhea and anorexia. Mean peak and trough concentration with chronic dosing in all cats were 46 and 59 mcg/ml, respectively, with concentration at 42, 59 and 79 in cats with adversities. Zonisamide appears to be minimally involved in drug interactions typical highly protein-bound drugs. However, it is involved with interactions involving CYP enzymes. Nakasa demonstrated clearance was decreased 31%, 23% and 17% by ketoconazole, cyclosporine A and miconazole, respectively; fluconazole inhibited clearance to a lesser degree but itraconazole appeared to have no effect.

Table1. Therapeutic drug monitoring data for drugs in dogs or cats

Drug	Dose[1] mg/kg	Route	Interval	Halflife	Time to SS[2]	Therapeutic Range (3) Low	High	Units
Bromide	20	PO	12-24hrs	21d	2-3m	1	3	mg/ml
Clorazepate	0.5-1	PO	8 hrs	4-6 (h)	<24 hrs	150[3]	400	ng/ml
Diazepam	1-2	PO	8 hrs		<24 hrs	150[3]	400	
	0.5-2[4]	IV	5-10 min					
	5 to 20[5] total	IV inf	60 min					
Felbamate	15	PO	divided bid	5-8 (d)	<24 hrs	30	60	mcg/ml
Gabapentin	10-30	PO	8-12	< 14 h	2 – 3 days	12	21	mcg/ml
Leviteracetam	20 mg/kg	PO	8	2-8h		6	21	mcg/ml
Phenobarbital	2	PO	12 hrs	app 72	2 to 3 w	20	45	mcg/ml
	3-6	IM		(9-12; d)	2-3 days			
	6-12[8]	IV slow	3 mg/kg increments to effect					
Zonisamide	4-6	PO	8-12	16-44*	2-3 days	10	40	mcg/ml

Zonisamide does not appear to affect its own metabolism nor the metabolism of other drugs in animals or humans. Phenobarbital will shorten zonisamide half-life. The impact of 35 days of dosing phenobarbital on the disposition of zonisamide was studied in dogs. Unfortunately, all data was pictorially represented, limiting assessment of changes in disposition.[217] After 35 days administration of phenobarbital, concentrations appeared to decrease to about 2.75 mcg/ml, returning to 3.5 only after approximately 12 weeks after phenobarbital was discontinued. The decrease in half-life appeared to approximate 3 hrs or approximately 30%. Phenobarbital shortened the half-life of zonisamide from 27 to 36 hours in humans, resulting in lower plasma drug concentrations.[218] The impact of phenobarbital does not appear to be profound, but monitoring is warranted and for some patients, collection of both a peak and trough sample might be warranted in patients receiving phenobarbital with zonisamide.

As a sulfonamide, zonisamide inhibits thyroid synthesis of thyroid hormones. Anticonvulsants (phenytoin) may also have a direct negative effect on TSH response to TRH. Drug-induced changes in T_4-binding globulins have also been documented in human patients taking anticonvulsants. Boothe demonstrated that zonisamide dosed for 8 weeks was associated with a decrease in total T4 below normal limits. Free T4 and TSH were also decreased from pre-treatment concentrations, although both were within normal limits. Zonisamide concentrations were higher than the recommended therapeutic range. Thyroxin and TSH concentrations might facilitate diagnosis of hypothyroidism in animals receiving zonisamide. Note that thyroid supplementation suppresses response to TSH, and testing should not be performed until supplementation has been discontinued for 4 to 6 weeks.

Clinical reports of zonisamide use in animals are limited. In one report, zonisamide was effective in reduction of seizures in patients with epilepsy that had not sufficiently responded to one or more anticonvulsants (including phenobarbital and/or bromide) in 7/12 dogs at

doses designed to achieve 10 to 40 µg/ml. Dose reduction or discontinuation of concurrent anticonvulsant was possible in 8/12 dogs. Mean concentrations approximated 20 µg/ml; mean dose was 9 mg/kg every 12 hrs.[219] A second open clinical trial studied zonisamide for treatment of refractory seizures in dogs (n=13).[220] Mean reduction in seizure was 70%, with three dogs relapsing. Drug concentrations were not measured.

Gabapentin is an anticonvulsant approved in 1994 for treatment of partial seizures with or without generalization in humans with epilepsy.[157,159] It has been used in dogs and anecdotally in cats. It appears to act by a novel mechanism by promoting the release of GABA, although the actual mechanism of release is not known. Among its attributes is antagonism of N-methyl-D-Aspartate receptors, contributing to is potential efficacy for control of chronic pain. Although gabapentin is absorbed well after oral administration, its absorption appears to be dose dependent, relying on a saturable transport process. This process has been cited as the reason that AED effects last longer than anticipated based on drug half-life, allowing twice daily administration. In contrast to bromide, the short half-life of gabapentin (in humans) results in steady-state concentrations within 24 to 48 hours. The drug is eliminated in people entirely by renal elimination, thus avoiding some of the risks of hepatotoxicity and drug interaction. The drug is sufficiently safe that TDM is not necessary; rather, the dose is increased as needed to control seizures. Mild dizziness, nausea, and vomiting have occurred in a small percentage of human patients.

Gabapentin studies with animals are limited. Gabapentin has been studied in the dog following oral administration of 50 mg/kg. Oral bioavailability was 80% and plasma protein binding was <3%. Mean intravenous elimination half-life of 2.9 hr has been reported in dogs. Repeated administration did not alter gabapentin pharmacokinetics nor did gabapentin induce hepatic drug metabolizing enzymes. In the dog, 34% of the dose was metabolized to the N-methyl form. The principal route of excretion was the urine.[162,163] A more recent study compared gabapentin (600 mg to Beagles) after oral administration of either an immediate or slow release product.164 The sustained release product did not disintegrate, but the release kinetics were not substantially different from the immediate release product.

The addition of gabapentin (35 to 50 mg/kg divided every 8 to 12 hr) to either phenobarbital or bromide was studied in epileptic dogs (n=17) using an open, uncontrolled design. The interictal period increased, but the number of seizures did not. However, seizures were eradicated in 3 dogs. Side effects evolving with the addition of gabapentin included sedation, which resolved within several days, and hind limb ataxia which resolved with a reduction in the bromide dose.[165] One of the major disadvantages of this drug is its expense. Gabapentin may not be effective for the control of epilepsy when used at doses extrapolated from human patients. Clinical trials are indicated to establish the most appropriate dosing regimen for

dogs or cats. Gabapentin is among the drugs for which status epilepticus may occur during withdrawal.

Imepitoin, an imidazoline derivative, has been approved for treatment of canine epilepsy in Europe and has recently been approved for use in the USA in dogs for treatment of noise aversion. Imepitoin is a low-affinity partial agonist at the benzodiazepine GABAa receptor and its action is unique among current anticonvulsants. This mechanism offers several advantages compared to full agonists, including less severe adverse effects and a lack of tolerance and dependence liability in rodents, dogs, and nonhuman primates. In a recent study of experimental epilepsy imepitoin was slightly less potent than phenobarbital in increasing seizure threshold but had fewer adverse side effects.

In a blinded parallel study of 226 client-owned epileptic dogs the administration of imepitoin twice daily in incremental doses of 10, 20 or 30 mg/kg demonstrated comparable efficacy to phenobarbital in controlling seizures.

The Older Tried and True?

Benzodiazepines: Diazepam is the model benzodiazepine. Like, phenobarbital, it is a GABA agonist and decreases the spread of seizures. Like phenobarbital, it is a schedule IV drug. An advantage of this drug is that it decreases spinal reflexes. An advantage to this is that it helps decrease the impact that tonic clonic muscle contraction might have on hyperthermia. However, a major disadvantage to most benzodiazepines in dogs, including diazepam, is that dogs develop tolerance to the anticonvulsant effects. As such, it cannot be used for chronic control and its use is limited in dogs to acute management. In cats, it is toxic. Diazepam is well absorbed orally, but it undergoes first pass metabolism and as such, has a very short half-life. It distributes so rapidly into the CNS that it is the first choice for acute management of status epilepticus or cluster seizures. However, it is metabolized to active metabolites which, although less effective than diazepam, have a longer half-life. The combined effect of these metabolites prolongs the duration of effect of diazepam. Nonetheless, it still has a half-life that is sufficiently short that constant rate infusion may be necessary for acute seizure management. Diazepam is available as oral or IV preparations but only the solution is likely to be used. The IV preparation can be given in an emergency rectally. Adverse events are largely limited to cats but include what is an idiosyncratic reaction manifested as (probably lethal) hepatic failure. The incidence is high enough that this drug should not be used in cats. Note that a number of other benzodiazepines are used in animals. Among them is alprazolam which is used for behavior management for control of anxiety.

Bromide. Bromide continues to be a drug of choice for first choice or combination anticonvulsant therapy in dogs. For rapid response, a loading dose can be given but it is important to match the loading dose with an appropriate maintenance dose, otherwise, drug concentrations will slowly decline over 2–3 months (with the majority of the decline in 15–21 days). A load of 450 mg/kg should yield concentrations of 1 mg/ml (the minimum end of the therapeutic range); for each 0.5 mg/ml increase in blood concentrations desired (maximum end of the range is 3.5 mg/ml), an additional 225–250 mg/kg loading dose should be given. If this loading dose is split over 5 days, the maintenance dose should also be given (30 mg/kg/day for 1 mg/ml; 15 mg/kg/day for each 0.25 to 0.5 mg/ml increase above that). Patients should be monitored 1 to 3 days after the loading dose and again at one month; if the two samples do not match, the maintenance dose should be changed accordingly. Our lab will increase bromide concentrations well above the recommended range if necessary to control seizures as long as the animal is not groggy or otherwise is intolerant to the drug. If groggy, our choice is to decrease phenobarbital concentrations first. Phenobarbital can be completely eradicated in some animals; in contrast, some animals will be controlled only at concentrations of both bromide and phenobarbital at the maximum end of the therapeutic range. Bromide can be made by dividing a 1kg bottle of the salt into 4 equal 250 gm parts (store in zip lock back, protect from humidity). One package can be added to a 1 liter bottle of commercial spring water: Draw a line at the 1 liter mark, remove about 0.5 liter, add the bromide, and enough water to make the bromide dissolve, and fill the remaining volume to the line with either water or corn syrup for flavoring. The final solution is 250 mg/ml. Potassium bromide can be loaded following rectal administration over a 24 hour period (divide the loading dose into 4 administrations). IV administration is not recommended because of the risk of potassium overload.

Bromide has been studied in cats (as the potassium salt) when used at the canine maintenance dose. Although concentrations are similar to those achieved in dogs, in a retrospective study of 17 cats, 38% of seizuring cats developed signs consistent with feline bronchial asthma. The time to onset varied from 3 to 24 months and did not seem to be related to dose. Treatment with glucocorticoids may be helpful. Combination anticonvulsant therapy is a powerful tool for control of refractory seizures (defined as unacceptable seizure activity despite anticonvulsant concentrations at the maximum end of the therapeutic range). Several options exist. We have studied bromide as an add-on anticonvulsant and found it to be effective in eradicating seizures in 60% of dogs, refractory to phenobarbital. Bromide is also effective as a sole anticonvulsant. Efficacy and safety of bromide (BR) were compared to phenobarbital (PB) in 46 dogs with spontaneous epilepsy using a parallel, randomized double blinded study design. Acceptance was based on seizure history, physical and neurologic examinations and clinical pathology. Dogs were loaded over a 7 day period to achieve the minimum end of the therapeutic range of the assigned drug. PB (3.5 mg/kg) or

BR (15 mg/kg) was administered every 12 hours. Data (clinical pathology and drug concentrations) were measured at baseline and at 30 days intervals for 6 months. All but 3 patients completed the study. Seizures initially worsened in 3 dogs on BR but not in any PB patient. Mean seizure number, frequency and severity were reduced at 6 months compared to baseline for both drugs; seizure duration was shorter for PB but not BR. Seizure activity was eradicated in a greater percent of PB (85%) compared to BR (65%) patients, but successful control (at least 50% reduction in seizure number) did not differ between drugs at 6 months. Mean bid dose and drug concentrations were dose 4.1+1.1 mg/kg and 27+6 g/ml, respectively for PB and 31+11 mg/kg and 1.9+0.6 mg/ml for BR. Both drugs caused abnormal behaviors. Weight increased by 10% in both groups. Changes in clinical pathology were limited to increased (but within normal) serum alkaline phosphatase and decreased (but within normal) serum albumin at 6 months for PB compared to baseline and compared to BR at 6 months. Side effects at one and six months, respectively for each drug were: ataxia (PB: 55 vs. 5%;BR: 22 vs. 9%), grogginess (PB: 50 vs. 5%; BR: 35 vs. 13%), polydipsia (PB: 40 vs. 0%; BR: 39 vs. 4%), polyuria (PB: 35 vs. 0%; BR: 13 vs. 0%), hyperactivity (PB: 35 vs. 10%; BR 43 vs. 4% [one failure]), polyphagia (PB: 30 vs. 0%; BR: 43 vs. 4%) and vomiting (PB: 20 vs. 0%; BR: 57 vs. 21% [one failure]). One PB dog failed due to neutropenia, a reported rare side effect (as is superficial necrolytic dermatitis in dogs.) The incidence of grogginess and vomiting were greater in BR compared to PB at 6 months. This study suggests that both PB and BR are reasonable first choices for control of epilepsy in dogs, although PB may provide better control. Side effects can be expected to be greater in BR following chronic dosing.

Phenobarbital: Phenobarbital might be considered a broad-spectrum anticonvulsant. It is gabaminergic, but also targets glutamate (decrease) and calcium fluxes. Despite introduction of new antiepileptic drugs, phenobarbital has generally been the anticonvulsant of choice for the cat and dog. In a clinical trial by the author, efficacy when supported by monitoring (defined as eradication of seizures) was 85%. It is effective in all types of epileptic seizures observed in cats and dogs. This may change with neurologists' preference with the apparent safety and success of zonisamide. It is a broad spectrum anticonvulsant. Well absorbed orally, it takes about 15 minutes to distribute into the CNS and thus, while useful for treating emergency seizures, does take more time to be effective compared to diazepam. Approximately 16 days (8 to 15.5 days) of multiple dosing is necessary to attain steady-state serum concentrations in the normal (uninduced) animal; however, induction may cause this period to be shorter after a change in the dosing regimen of an animal already receiving phenobarbital. It is metabolized in the liver to largely inactive, although potentially (author opinion) toxic metabolites. Hepatic metabolism impacts therapeutic success both because of the potential for hepatotoxicity at high concentrations (the author avoids higher than 35 to 40 mcg/ml), but also drug interactions. Phenobarbital is likely to induce or increase the

clearance of any other drug metabolized by the liver, including itself and zonisamide (and possibly levetiracetam). This contributes to the marked variability that characterizes its half-life. We have measured elimination half-lives longer than 72 hours and shorter than 12 hours, the latter occurring in about 10% of patients. For the latter patients, subtherapeutic concentrations may occur during a dosing interval. For the former, the time to steady-state may take 2 weeks or more. It is a controlled substance, complicating convenient use.

Patients should not considered refractory to phenobarbital therapy until plasma concentrations reach 35 to 40 µg/mL unless unacceptable side effects persist at lower concentrations. However, because of the potential for phenobarbital-induced hepatotoxicity, the author often recommends adjuvant therapy once phenobarbital concentrations exceed 25 µg/mL in an uncontrolled dog.

Polyphagia, polydipsia, and polyuria are side effects that occur in animals receiving clinical dosages of phenobarbital. The polyuric effect is apparently due to an inhibitory action in the release of antidiuretic hormone.[70] Identical sedative side effects are observed in the dog after treatment with phenobarbital or primidone (discussed later).[17] Dogs appear fatigued and listless after receiving either drug; some are weak in the rear legs, and ataxia occurs. All of these effects may be long lasting and may persist in some cases for the duration of treatment; however, tolerance to these effects generally develops in most dogs 1 to 2 weeks after initiating the dosing regimens. Phenobarbital can cause what is an apparent allergic reaction manifested as a bone marrow dyscrasia in dogs. Pancytopenia or (more commonly) neutropenia is detected after a complete blood count in animals that presented with a variety of clinical signs. Bone marrow suppression generally resolves rapidly once phenobarbital is discontinued.[71] Bone marrow necrosis also has been associated with phenobarbital.[72] Care should be taken to begin an alternative anticonvulsant drug (e.g., bromide) in animals that are at risk for worsening of seizures should phenobarbital be rapidly discontinued. It is likely that a metabolite is the cause of the dyscrasia; as such, an anticonvulsant minimally metabolized by the liver may be a wiser choice for drug replacement. Phenobarbital can induce tissue (peripheral tissues and the liver) metabolism of thyroid hormones. Serum total thyroxine (T4), total triiodothyronine (T3), free T4, and thyroid-stimulating hormone (TSH) concentrations were compared in epileptic dogs (n=78) with seizure disorders and treated with phenobarbital (n=55), phenobarbital and bromide (n=15), and bromide (n=8) and clinically normal dogs (n=150). Whereas T3 and TSH total did not differ among groups, total and free T4 were lower in phenobarbital and phenobarbital plus bromide compared with concentrations in clinically normal dogs. In a second study of experimental dogs (n=12), Gieger and coworkers[76] demonstrated that phenobarbital at 4.4 to 6.6 mg/kg administered orally twice daily for 27 weeks resulted in significant decreases in serum T4 and free T4 and increased TSH. These changes persisted for up to 4 weeks after discontinuation of therapy.

Thyroid screens in apparently normal animals that yield results indicative of hypothyroidism do not necessarily indicate the need for treatment; indeed, overtreatment may result in undesirable CNS stimulation. On the other hand, if an animal presents with clinical signs consistent with hypothyroidism, replacement therapy may be indicated.

At high plasma drug concentrations (i.e., more than 30 to 40 µg/mL), phenobarbital appears to be hepatotoxic.[77] Animals whose liver is induced and thus requires high doses of phenobarbital to maintain drug concentrations in the lower therapeutic range may also be more susceptible to toxicity because of increased formation of metabolites. Phenobarbital will also cause nonpathologic changes in hepatic clinical laboratory tests because of induction of enzymes. Serum alkaline phosphatase (SAP) and the transaminases are likely to increase with chronic therapy. Whether or not this is indicative of liver disease is controversial; hepatic function tests should be measured at baseline and if liver disease is of concern. Bilirubin has not been a sensitive indicator of liver disease induced by phenobarbital in the author's experience. The risk is increase if additional drugs metabolized by the liver are administered at the same time. Phenobarbital has been associated with hypertriglyceridemia in dogs.[37] Median fasting serum triglyceride (mmol/L) was 0.6 (range 0.9 to 1.6) for phenobarbital (n=28) and 0.6 (range 1.2 to 3.6 mmol/L). Phenobarbital may be associated with pancreatitis. Although studies have focused on bromide, studies supporting this association have documented an increased risk in patients receiving both bromide and phenobarbital, as well as phenobarbital alone.[80,81]

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