SEARCH AND SEIZURE: LOOKING FOR NEW ANTICONVULSANT OPTIONS?

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Seizures are common in small animals, particularly dogs. Although traditional maintenance anticonvulsant drugs (e.g., phenobarbital, primidone, bromide) are reasonably effective in controlling seizures, a substantial proportion of dogs (20-40%) are refractory to monotherapy with these medications. In addition, adverse effects are common with administration of these drugs, and in some cases, can be life-threatening. As a result, there is considerable interest in newer medications that might offer improved efficacy or therapeutic indices. Although several anticonvulsants were licensed for use in humans in the 1950s, 1960s and 1970s (e.g., phenytoin, carbamazepine, valproic acid), pharmacokinetic limitations have curtailed use in veterinary species, and no new anticonvulsants were licensed in the United States from 1978-1993. However, since 1993 there has been a virtual explosion of new anticonvulsants developed for use in humans. Of these, a subset has suitable pharmacokinetic and toxicity profiles allowing use in dogs and cats.

PHENOBARBITAL

Year developed or licensed: 1912
Mechanism of action: primarily functions as a gamma-aminobutyric acid (GABA) agonist
Starting dose: 2.5-3.0 mg/kg q 12 hours
Reported therapeutic serum concentrations: 15-35 μg/ml
Parenteral formulation commercially available? Yes

Phenobarbital is the most widely used anticonvulsant in veterinary medicine, and has been utilized in humans and animals for more than a century. Although it has been reported to act through a variety of mechanisms, its primary mode of action is as a GABA agonist, which leads to opening of ligand-gated chloride channels and hyperpolarization of neurons. This hyperpolarization reduces the likelihood of an action potential occurring in affected cells. When given as a regular maintenance dose, steady state is achieved after 2 weeks in most dogs, although some will take up to 4 weeks. Phenobarbital is extensively metabolized by the liver but is also a potent inducer of hepatic microsomal enzymes. As a result, it can increase the metabolism of drugs metabolized by this system, including other anticonvulsants (and itself) over time. Therapeutic serum concentrations are generally reported to be 15-45 μg/ml although exceeding concentrations of 35 μg/ml is not recommended due to the increased risk of hepatic injury (see below). Monitoring of therapeutic concentrations is absolutely necessary with this drug both to prevent increased seizure frequency if the concentration drops below the therapeutic level but perhaps more importantly in order to avoid high concentrations that may predispose the patient to hepatic injury.

Common adverse effects of phenobarbital include polyphagia, polyuria, polydipsia, sedation, pelvic limb ataxia and weakness. Paradoxical hyperactivity is rarely seen. The potential for phenobarbital to cause or predispose to pancreatic inflammation has also been suggested.[1,2] Hepatic injury (including hepatic failure) is a well-known adverse effect that is correlated with the serum concentration of the drug, but can be reversible with drug discontinuation. Bone marrow toxicosis leading to thrombocytopenia or neutropenia is an uncommon but potentially devastating adverse effect of phenobarbital administration. Unlike hepatic toxicosis, these blood dyscrasias are idiosyncratic and unrelated to dose or serum concentration of the medication.

BROMIDE

Year developed or licensed: not synthesized (an element); anticonvulsant properties discovered in 1850s
Mechanism of action: mimics action of chloride in neurons by preferentially entering chloride channels
Starting dose: 40-50 mg/kg/day as monotherapy; 20-30 mg/kg/day when added to phenobarbital
Reported therapeutic serum concentrations: 1000-3000 μg/ml (or 100-300 mg/dl or 1-3 mg/ml)
Parenteral formulation commercially available? No

Bromide is a compound containing bromine, a halogen element similar to chlorine (and located right below it in the periodic table). It behaves similarly to chloride in the body, and appears to preferentially enter chloride channels within neurons, leading to neuronal hyperpolarization and inhibition of neuronal firing. This similarity to chloride also results in competition between the two elements for binding sites (for uptake or excretion); this has a practical clinical effect, as the salt content (i.e., NaCl) of the diet should remain constant whenever bromide is administered to avoid fluctuations in serum concentrations. The elimination half-life of bromide from the body is extremely long, and as a result steady state takes 3-4 months to achieve in the dog.

As the mechanism of action is similar to phenobarbital, common adverse effects are similar, including polyphagia, polyuria, polydipsia, sedation, pelvic limb ataxia and weakness. Pancreatitis has also been documented, and may be more common when used in combination with phenobarbital.[3] As the drug is a salt, straight oral administration as a liquid can lead to vomiting, and therefore administration with food is recommended. Bromide results in an unusual infiltrative eosinophilic bronchial disease in a large proportion of cats, and use in this species is not recommended.

FELBAMATE

Trade name: Felbatol
Year developed or licensed: 1993
Mechanism of action: GABA agonist, NMDA receptor antagonist
Starting dose: 15-20 mg/kg q 8 hours
Reported therapeutic serum concentrations: not routinely used
Parenteral formulation commercially available? No

Felbamate was approved for use in humans in the United States in 1993. It is often considered to be a "broad spectrum" anticonvulsant, with multiple potential mechanisms of action including acting as a GABA agonist and NMDA receptor antagonism (which blocks glutamate neurotransmission). It has been used successfully as a monotherapy in dogs with seizures.[4] Felbamate has been associated with two rare but devastating adverse effects in humans, aplastic anemia and hepatic failure. The expense associated with its administration as well as concerns with hepatic toxicity (particularly when used in combination with phenobarbital) has limited the use of felbamate in veterinary patients.

GABAPENTIN

Trade name: Neurontin

Year developed or licensed: 1994
Mechanism of action: inhibits voltage-gated calcium channels
Starting dose: 10-30 mg/kg q 6-8 hours (dog) or q 8-12 hours (cat)
Reported therapeutic serum concentrations: not routinely used
Parenteral formulation commercially available? No

Together with felbamate, gabapentin was one of the earliest of the new generation of anticonvulsants licensed for use in the early 1990s. Although originally developed to mimic GABA, it does not exert its therapeutic effects through this mechanism, instead inhibiting voltage-gated calcium channels and interfering with neurotransmitter release at the pre-synaptic terminal. In humans, gabapentin is not substantially metabolized in the body although dogs seem to metabolize this drug to some degree. However, there are no substantial drug-drug interactions. Gabapentin is a very safe medication, and reported adverse reactions in veterinary patients are mainly limited to sedation.

TOPIRAMATE

Year developed or licensed: 1996
Mechanism of action: inhibits voltage-gated sodium channels, augments GABA activity, AMPA/kainate receptor antagonism, carbonic anhydrase inhibition
Starting dose: 2-5 mg/kg q 12 hours, escalate as needed
Reported therapeutic serum concentrations: not routinely used
Parenteral formulation commercially available? No

Topiramate acts through several potential mechanisms and is considered to be a "broad spectrum" anticonvulsant. There are no published reports of its use in epileptic dogs or cats, and the elimination half-life in dogs is very short, which raises concerns about the ability to achieve therapeutic blood concentrations with twice or even thrice daily dosing. Despite these concerns, topiramate is used by some clinicians to treat seizures in these species with anecdotal success.

LEVETIRACETAM

Year developed or licensed: 1999
Mechanism of action: binds SV2A, a synaptic vesicle protein
Starting dose: 20 mg/kg q 8 hours (intermediate/standard release); 20-30 mg/kg q 12 hours (extended release), escalate as needed
Reported therapeutic serum concentrations: 5-45 μg/ml
Parenteral formulation commercially available? Yes

Levetiracetam was first licensed for use in humans in the United States in 1999, and was unique among the newer medications at the time in providing formulations for both oral and parenteral (intravenous) administration. It has a unique mechanism of action, presumably interfering with neurotransmission by blocking a protein responsible for docking of the synaptic vesicles to the cell membrane prior to neurotransmitter release (SV2A). Levetiracetam is thought to be excreted without being metabolized in humans, although dogs appear to metabolize the drug to a certain degree; this has become evident in dogs concurrently receiving phenobarbital, where therapeutic serum concentrations are reduced.[5] The assessment of therapeutic serum concentrations in clinical patients is possible, although this drug is often escalated if seizure control is suboptimal. Levetiracetam is a very safe drug, and adverse effects reported to date in veterinary patients are mainly limited to sedation.

ZONISAMIDE

Year developed or licensed: 2000
Mechanism of action: inhibits voltage-gated sodium channels
Starting dose: 3-5 mg/kg q 12 hours as monotherapy; 10 mg/kg q 12 hours when added to phenobarbital
Reported therapeutic serum concentrations: 10-40 μg/ml
Parenteral formulation commercially available? No

Zonisamide was first developed in Japan, and was subsequently approved for use in humans in the United States in 2000. Its primary mechanism of action appears to be inhibition of voltage-gated sodium channels, which interferes with propagation of the action potential and repetitive neuronal firing. Zonisamide is hepatically metabolized, and its metabolism is affected by the concurrent administration of phenobarbital.[6] Steady state is achieved after 4 days. Adverse effects are primarily limited to sedation, inappetence, vomiting and diarrhea, with the gastrointestinal effects seen more commonly in cats. However, idiosyncratic hepatic failure has been reported in several dogs after administration of this drug,[7] although this appears to be very rare, and was reversible in one case after discontinuation of the medication.[8] Other rare suspected adverse effects have included neutropenia, polyarthritis, uveitis and immune-mediated anemia.[9,10]

PREGABALIN

Year developed or licensed: 2004
Mechanism of action: inhibits voltage-gated calcium channels
Starting dose: 2 mg/kg q 12 hours escalating to 3-4 mg/kg q 8-12 hours
Reported therapeutic serum concentrations: not routinely used
Parenteral formulation commercially available? No

Pregabalin represents the first drug released utilizing a new trend of anticonvulsant development, where a proven anticonvulsant's chemistry (in this case gabapentin) is altered in order to improve some aspect of its pharmacokinetics, pharmacodynamics, metabolism or adverse effect profile. Pregabalin has a similar mechanism of action to gabapentin, but a greater affinity for its target and is a more potent anticonvulsant (and analgesic). Metabolism and drug interactions are minimal. Administration to veterinary patients has been somewhat limited until fairly recently due to expense, but there are reports of its use in both dogs and cats.[11,12] It also appears to be a very safe drug, although the sedative effects seem more profound than with gabapentin.

PRACTICAL USE OF NEWER ANTICONVULSANTS

There are very few published studies evaluating the use of newer generation anticonvulsants as monotherapy in veterinary patients, although these suggest that such a strategy may be effective.[4,13] More commonly, reports describe open-label trials with very small numbers of dogs that are refractory to conventional anticonvulsant therapy, with an apparent response after the addition of one of these newer medications.[11,14-16] However, one must be careful in the interpretation of such reports, as a placebo effect may be responsible for some of the beneficial effect.[17] It has been harder to show a clear benefit with the addition of these drugs to refractory canine epileptics in larger randomized and blinded clinical trials.[18] In the author's opinion, there are two main reasons to consider the use of newer generation anticonvulsant medications:

1) These drugs have a variety of mechanisms of action, which appear to be different from traditional medications. Interfering with seizure initiation or propagation in a multimodal fashion may have advantages over using two drugs with the same (or very similar) mechanism.
2) Newer generation anticonvulsants have fewer adverse effects than traditional drugs. These side effects are mainly limited to sedation (which tends to be less severe than that seen with either phenobarbital or bromide) and gastrointestinal side effects (vomiting, diarrhea) with zonisamide. Felbamate is an exception, as there is concern with hepatic dysfunction, particularly when used in combination with phenobarbital.

Elimination half-lives of these newer medications are relatively short, and drug steady state levels are reached more quickly with administration of a regular oral dose (see Table 1). The main disadvantages of these newer drugs are their expense (although most are now available as a generic, and costs are decreasing) and the requirement for administration every 8-12 hours. Of these newer generation drugs, the author generally prefers to use zonisamide, levetiracetam or pregabalin. Assays to measure blood levels of these drugs are available, but these medications are often administered to effect. In some cases, success with the addition of an anticonvulsant drug may allow the eventual withdrawal of the initial medication, although this must be accomplished very gradually and with caution. The author frequently uses these newer anticonvulsant medications (particularly zonisamide and levetiracetam) as the second drug choice (typically instead of bromide), but also as initial monotherapy for newly diagnosed canine or feline epileptics.

There are several new anticonvulsants that have been either recently licensed for use in the United States or are in advanced stages of development. Of these, some are novel in terms of their chemistry and potentially their mechanisms of action (e.g., lacosamide, rufinamide) while in others the chemistry of a known anticonvulsant has been altered to improve efficacy or mitigate adverse effects (e.g., brivaracetam, fluorofelbamate). Although some pharmacokinetic information is available for select agents,[19] reports of the clinical use of these agents in veterinary patients are not yet available.

Table 1: Anticonvulsants for Use in Veterinary Patients

Medication	Initial Dose		Time to Steady State	Therapeutic Serum Concentrations	Comments
	Without phenobarbital	With phenobarbital			
Phenobarbital	2.5-3.0 mg/kg q 12 h	N/A	14-29 days	15-35 µg/ml	
Bromide	40-50 mg/kg/day	20-30 mg/kg/day	3-4 months	1000-3000 µg/ml	Do not use in cats
Zonisamide	3-5 mg/kg q 12 h	6-10 mg/kg q 12 h	3-5 days	10-40 µg/ml	
Levetiracetam	20 mg/kg q 12 h	Adjust based on serum concentration	1-2 days although may never reach true	5-45 µg/ml	Can escalate if needed (to 80 mg/kg or higher)

			steady state		
Gabapentin	10-30 mg/kg q 8 h		1-2 days	Not available	
Pregabalin	2-4 mg/kg q 8-12 h		2-3 days	Not available	Start at 2 mg/kg and escalate

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