Part I: Zonisamide and Levetiracetam for adjunctive seizure management.

Phenobarbital (PB) and potassium bromide (KBR) are the drugs most veterinarians choose as the initial therapy for seizures. Phenobarbital seems to provide the most reliable seizure control for the most patients with generally few adverse effects (blood dyscrasias, hepatotoxicity, superficial necrolytic dermatitis, dyskensis), which are reversible if caught early. Potassium bromide is also a good anticonvulsant, although not as reliable as phenobarbital. Adverse effects (pancreatitis, panniculitis, and anecdotally, megaesophagus) are rare. Gastroenteritis is more common but can usually be managed by dividing the dose and giving it with food. KBr should not be used in cats due to the risk of life threatening eosinophilic pulmonary infiltrates causing an asthma-like condition.

Both KBr and PB have inconvenient side effects (sedation, pelvic limb weakness, PU/PD and polyphagia), therefore it may be desirable to choose an alternative adjunctive therapy when a patient is failing one of these first line therapies.

Zonisamide and leveiracetam are now generic and have become far less expensive. In my experience, they tend to be less reliable when used as the sole anticonvulsant and are better reserved for adjunctive therapy.

Zonisamide is a sulfonamide-based drug and a weak carbonic anhydrase inhibitor. It inhibits voltage gated sodium channels and T-type calcium channels, enhances GABA release and inhibits glutamate release. It is 70% bioavailable and mostly excreted in the urine. About 20% is metabolized, primarily in the liver. Therefore, coadministration of phenobarbital will increase its clearance. The half-life is 15-20 hours in the dog (steady state will be achieved in 3-4 days) and 33 hours in the cat (ss 6 days). The dose range for dogs is 3-12 mg/kg BID, and for cats 5-20mg/kg SID-BID. We typically start both at 8-10mg/kg BID. It comes in 25, 50, 100 mg capsules. We really appreciate minimal side effects in our patients, however sedation, ataxia, gastrointestinal upset and weight loss reported.6 Possible adverse reactions include those associated with other sulfa drugs such as immune disease (KCS, polyarthritis, IMHA), and there have been two cases of apparent hepatotoxicity and one case of renal tubular acidosis attributed to zonisamide therapy.

Levetiracetam is a pyrrolidine-based anticonvulsant whose mechanism has not been fully elucidated. It does work at synaptic vesicle protein 2A to reduce presynaptic neurotransmitter release (regulates exocytosis) but it may have more than one mechanism of action. It is 100% bioavailable, and even though there is no apparent hepatic metabolism, there is increased clearance when used in conjunction with Phenobarbital. The reason for this is not understood. It is 70% eliminated in urine, and the remainder is hydrolyzed in serum and organs other than the liver.6 The half-life in dogs is 3-4 hours and in cats 2-4 hours. The recommended starting dose is 20mg/kg TID. It comes in 100mg/ml oral solution, 250mg, 500mg, 750mg and 1000mg tablets and 100mg/ml IV solution. The greatest disadvantage is the necessity for TID dosing. If the patient is 20 kg or greater extended release tablets may be used at 20 mg/kg BID (500mg, and 750mg formulations). Of course, these tablets should not be split. Some clients have reported seeing the tablets undigested in feces, so they may not work well in all dogs.

Levetiracetam is very safe; even at 6 x the dose the side effects (salivation, restlessness, ataxia, vomiting) resolved within 24 hours.6 At regular doses it has no greater side effects than placebo in dogs. Levetiracetam appears to have a “honeymoon effect” in many veterinary patients. It works well initially but then tolerance develops within several months and it becomes ineffective. The study reporting this finding, noted tolerance in 6/9 patients by 8 months of therapy.
Auburn University, College of Veterinary Medicine can assay serum drug levels for both. Peak and trough levels are ideal with the rapidly metabolized levetiracetam. Drug levels are expensive and usually reserved for patients that are unusually sedate (may be experiencing an overdose) or have poor control of seizures despite increasing doses.

Look for Part II of this article on strategic anticonvulsant use in the next Connected newsletter.


Takikawa S, Muto M, Mishima K, Egashira N, Fujiwara M.


