

What's New? Introducing the availability of either zonisamide (Zonegran®) or levetiracetam (Keppra®) monitoring by the Clinical Pharmacology Laboratory at Auburn University (<http://www.vetmed.auburn.edu/index.pl/clinpharmlab>). This is a preliminary period of availability, testing the waters to determine if the demand for monitoring is sufficient to pay the cost of setting up and maintaining the assay. The assay involves HPLC and accordingly, is more expensive than either bromide or Phenobarbital. Our ultimate goal is to reduce the current cost of \$80 to less than \$70 for both assays. This will require an increase in number (for each sample, since the assay is not automated, we must generate a standard curve and controls, running up to 7 additional samples for each patient sample). During this introductory period for levetiracetam, the cost will be \$50, with the price increase to \$80 anticipated in January.

Why should you monitor these drugs? Despite the (assumed) safety of these drugs in dogs or cats, monitoring should be considered. Safety is not the sole reason we monitor any drug. The risk of therapeutic failure is a more compelling reason for monitoring anticonvulsant drugs. The lack of an animal therapeutic range should not deter monitoring: therapeutic ranges established in humans have offered reasonable targets for other drugs. Further, a therapeutic range is simply a population statistic that indicates the range in which most patients are likely to respond. However, monitoring can be used to identify the individual patient's therapeutic range. The availability of baseline concentrations provides a target in the event of future therapeutic failure, a means to identifying worsening of underlying disease, decreased drug concentrations, or drug interactions. Further, although both drugs are safe, and failed response can be addressed by dose increases, if a patient is at the maximum end of the therapeutic range, the more prudent approach to adjusting therapy is the addition of a second (third) anticonvulsant. Monitoring can help identify that point. As with other anticonvulsants, variability in drug disposition should be expected, indicating that concentration can not be predicted based on dose. Indeed, we have measured marked variability in the samples thus far submitted.

Monitoring results are most helpful when accompanied by recommendations. Note that the results of any sample submitted directly to the Clinical Pharmacology Laboratory at Auburn University (that is, not through a diagnostic laboratory) will be accompanied by recommendations offered by a veterinary clinical pharmacologist. Prices are cheaper for direct lab submissions as well (the diagnostic laboratory intermediary cost is avoided).

Why should either drug be used? These drugs should not necessarily be used in lieu of current anticonvulsants in dogs (Phenobarbital or bromide) or cats (Phenobarbital). Both zonisamide and levetiracetam are approved for use to treat epilepsy in humans. Pre-clinical studies with either drug has shown efficacy in animal models of experimentally-induced seizures. Both drugs are currently being studied by various investigators for applicability in animals with spontaneous epilepsy (see link). Either has been used in small animals as alternatives (to Phenobarbital or bromide) anticonvulsants. Although their use more commonly is as add-on anticonvulsants, increasingly each is being used as the sole anticonvulsant. Zonisamide (Zonegran®; 8 to 12 mg/kg divided

twice to three times daily, po) is a sulfonamide anticonvulsant approved for use to treat epilepsy in humans. Zonisamide appears to inhibit neuronal voltage-dependent sodium and T-type calcium channels. Additionally, ZNS modulates the dopaminergic system and accelerates the release of γ -amino butyric acid (GABA) from the hippocampus. Like phenytoin, ZNS is less likely to affect normal neuronal activity. A potential advantage of ZNS is free radical scavenging which protects against the destructive nature of radicals, especially in neuronal membranes. As with most sulfonamides, elimination includes both a hepatic (induced by Phenobarbital) and renal elimination. Its elimination half-life in dogs is 16 hours; accumulation in RBC and slow release allows twice daily therapy is reasonable. Therapeutic range recommended in humans is 10 to 40 (up to 61) mcg/ml. It has been used safely in combination with Phenobarbital for control of refractory seizures in dogs. Increasingly, it is being used as sole therapy for some dogs. As with any sulfonamide, at high concentrations (including those necessary to control seizures in some dogs), thyroid hormone synthesis will be impaired within several weeks of start of therapy. Function will return to normal but only when therapy is d/c. The protocol for thyroid hormone replacement, which is probably indicated once hypothyroidism has been documented, has not been well established. Levetiracetam (Keppra®) is an anticonvulsant approved for use in humans. Its mechanism of action is novel and does not appear to involve any known neurotransmitter, ion channel protein or receptors. A proposed mechanism of action is through binding to SV(synaptic vesicle)A2 receptors whose distribution is limited to neuronal and endocrine cells. 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. Accordingly, drug interactions should be minimal. However, it has a short half-life that is supportive of 8 hour dosing. It is being studied as an anticonvulsant for use in dogs or cats. However, it has been safely used in cats and dogs (20 mg/kg every 8 hrs po) as an add-on anticonvulsant and increasingly as sole therapy.