Zonisamide

Zonisamide (zoh-NIH-sah-mide) is the generic name (non-brand name) used in the United States for a widely used seizure medicine. The common brand name for Zonisamide is Zonegran (ZAHN-uh-gran).

ZONEGRAN® (zonisamide) is an antiseizure drug chemically classified as a sulfonamide and unrelated to other antiseizure agents.

Zonisamide was first used in Japan in 1972 to treat psychiatric diseases, and it has been widely used to treat epilepsy in Japan and Korea since at least 1990. The Food and Drug Administration (FDA) approved it for use in the United States in March 2000, suggesting that it be used along with other seizure medicines (as adjunctive or add-on therapy) in the treatment of partial seizures in adults.

Usually, Zonisamide is only prescribed as a lone treatment in cases where the patient is sensitive to phenobarbital or potassium bromide, or the pet’s owner doesn’t want to risk the potential side effects of those medications.

The exact means by which Zonisamide helps prevent convulsions is currently unknown, but it is believed that the medication effectively blocks calcium and sodium channels. This makes seizures less likely to occur in animals with epilepsy, and when they do occur, Zonisamide helps make them more manageable.

The use of Zonisamide is a controversial topic in the veterinary field. Because the medication is relatively new to veterinary use, many vets feel that the long-term effects of the medication on dogs and cats remain unknown. That said, many vets have used the medication with successful results.

Although it has been shown to be reasonably safe for canines and felines, Zonisamide does have the potential to produce certain side effects. The two most common side effects are sedation and ataxia, or a loss of muscle control. It can also cause diarrhea, vomiting, anorexia, and in rare cases, hyperthermia, skin reactions, and blood disorders.

Dosage and Administration of Zonisamide

The dosage and method of administration for Zonisamide should always be determined by your veterinarian. The prescribed dosage should be adhered to for the best possible results, as well as the pet’s safety. The average dosage for a dog with epilepsy is 8-12 mg/kg by mouth, every 8 to 12 hours. The most common formulation used for this medication is in sugar-coated oral tablet form.

There is suspicion that the liver enzyme induction that phenobarbital is famous for will speed up the metabolism of zonisamide. In other words, concurrent use of phenobarbital may speed up the removal of zonisamide from the body so that it does not work as well. This could lead to break-through seizures and is the reason why blood levels of zonisamide are commonly measured when there is concurrent use of phenobarbital. The starting dose of zonisamide is frequently higher for dogs on concurrent phenobarbital for this reason as well.

Because Zonisamide tablets feature a sweet outer coating, it is very important to keep the medication out of reach of children.

Case studies have been published where liver damage was reported in two dogs. Another case report involved a dog that developed a condition called renal tubular acidosis. Because zonisamide is relatively new to veterinary use, the risk of these serious conditions is unknown but because of these cases, relevant blood testing is recommended prior to starting zonisamide as well as periodically throughout therapy.

Zonisamide may reduce thyroid levels.

Temporal Lobe Epilepsy

Focal Impaired Awareness or Complex Partial Seizures
Refractory Seizures
Secondarily Generalized Seizures or Bilateral Tonic Clonic Seizure
Focal Aware or Simple Partial Seizure

Studies have shown that zonisamide works well when added to other seizure medications. Zonisamide is not a perfect add-on seizure medicine for everyone, however. Sometimes people must try a series of combinations before finding what is best for them.

Do not stop taking zonisamide without first checking with your doctor. Stopping the medicine suddenly may cause your seizures to return or to occur more often. Your doctor may want you to gradually reduce the amount of medicine you are taking before stopping it completely.

Allergic reactions
Approximately 1 in 20 people who take zonisamide have a red rash within the first few weeks of taking it. If this happens, tell the doctor or nurse right away, to be sure that it's not the beginning of a serious problem. It's rare for the rash to be serious, but don't ignore it. It's often necessary to switch to a different seizure medicine

On 2/23/2009, the US Food and Drug Administration issued a warning that the antiepileptic medication zonisamide (Zonegran) can cause metabolic acidosis in some patients. Metabolic acidosis is a condition of excess acidity (low pH) in the blood. The condition can manifest with a variety of symptoms, including chest pains, heart racing, rapid breathing, stomach upset, kidney stones, confusion and other symptoms.

CURRENT RESEARCH MANAGEMENT OF EPILEPSY GENETIC RESEARCH LITERATURE REVIEW ZONISAMIDE TRIAL

Adjunctive therapy for refractory canine idiopathic epilepsy

Many thanks to Dr Thilo von Klopmann from Dept. of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover who provided much of the information in this article.

Zonisamide is a new anticonvulsant licensed for man in the US in 2000 and recently studied for its efficacy as an add-on therapy for dogs with refractory epilepsy. It has a half life of about 15 hours in dogs (Matsumoto and others 1983, Thomas 2003). Most is excreted unchanged in urine although some hepatic metabolism occurs.

Zonisamide blocks voltage-dependent sodium and calcium channels and may reduce presynaptic glutamate release (Mac Donald 2002). Furthermore an increase in dopamine and serotonin levels in striatal and hippocampal structures are reported (Kaneko and others 1993, Okada and others 1995).

Zonisamide appears to be safe - few side - effects are reported in dogs, although mild ataxia and sedation may occur when treatment is started and vomiting and loss of appetite have been reported in some dogs (Dewey and others, 2004). An initial dose rate of 5 to 10 mg/kg BID is recommended - aiming for a serum concentration of 10-40 ug/ml. At a dose of 75 mg/kg body weight (four times the recommended dose) slight changes in blood count and an increase of liver weight were observed in one study (Walker and others 1988). Recently, however, in rats, an induction of tolerance has been described (Hamada and others 2001). This may be due to an induction of functional tolerance or an increasing severity of the epileptic process known as kindling phenomenon.

Limited data exist concerning the use of the anticonvulsant zonisamide in canine epilepsy (Dewey and others 2004, Boothe and others 2005, Saito and others 2005). A recent study by von Klopmann and others (2007) evaluated the efficacy of zonisamide as add-on to conventional anticonvulsant therapy in dogs with refractory epilepsy. In this study refractory epilepsy was defined as a lack of sufficient response to phenobarbital and/or potassium bromide treatment

despite therapeutic serum levels of one or both of these drugs. Zonisamide was administered as add-on therapy at a dosage of 10mg/kg body weight BID PO (Matsumoto and others 1983, Walker and others 1988, Boothe and others 2005, Saito and others 2005). Serum samples were collected from the dogs in the study at different time points following zonisamide administration and serum concentrations of drug were measured. The reference for zonisamide ranged from 10 to 40 µg/ml (Matsumoto and others 1983, Walker and others 1988).

Mild side-effects were noticed by the owners in six dogs after starting zonisamide therapy such as ataxia and sedation. Zonisamide is a sulphonamide-based anticonvulsant drug. Although not yet reported, clinicians should be aware of potential side effects similar to those associated with other sulphonamides.

The frequency and duration of seizures, as well as seizure severity, decreased in most of the dogs in this study following zonisamide administration. The high number dogs responding (at least a 50% reduction in seizures frequency) indicates a beneficial effect of zonisamide in refractory cases. Due to good seizure control in seven dogs a reduction of previous anticonvulsant therapy (phenobarbital, potassium bromide) was possible without subsequent impairment of seizure control. In several animals this led to a reduction in side effects and an improved quality of life. In one dog (a Border collie) dose reduction of conventional anticonvulsants resulted in a reduction of sedation so that breed typical behaviour was displayed again.

In a subgroup of the responder dogs an impairment of seizure control subsequently occurred. This loss of efficacy, after an initial good response, has been described for several drugs and has also been shown for zonisamide in rats (Hamada and others 2001).

The use of zonisamide is limited by its high costs and that it is not available in some countries. In the United States a generic form of active ingredient is available, however, there are no published studies describing the use of this formulation in dogs.

Further studies are warranted to evaluate the development of functional tolerance leading to a kind of “honey-moon effect” in zonisamide add-on therapy and the efficacy of zonisamide as monotherapy.

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New anticonvulsant drugs show promise in dogs, cats

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By Johnny D. Hoskins, DVM, PhD, DACVIM
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Q: Please review management of refractory seizure activity in dogs and cats.

A: Dr. C.W. Dewey gave an excellent lecture at the 2007 American College of Veterinary Internal Medicine Forum on "Recent and Upcoming Developments with the New Anticonvulsant Drugs." Here are some relevant points:

During the past 10 to 15 years, a number of new anticonvulsant drugs have been introduced for the treatment of human seizure disorders, some of which have been shown to be safe and effective for use in dogs. These drugs include gabapentin, felbamate, zonisamide and levitiracetam.

These anticonvulsant agents currently are used as an "add-on" drug for dogs with refractory seizure disorders. With the exception of levitiracetam, information on the use of such drugs in feline seizure disorders is anecdotal. But as these drugs get older and begin to emerge as less-expensive generic products, their clinical applicability in veterinary medicine continues to expand.

In general, these drugs have fewer side effects than the standard drugs, phenobarbital and potassium bromide, and are being considered more frequently as first-line anticonvulsant therapy for canine epilepsy. In addition to expanded use as maintenance anticonvulsant agents in dogs (and to a lesser extent in cats), two of these drugs (levitiracetam and zonisamide) have potential use in emergency settings (i.e., for *status epilepticus* and cluster seizures).

New anticonvulsant drugs

Gabapentin appears to exert its anticonvulsant effect primarily via interaction with neuronal voltage-gated calcium channels. Inhibition of these channels is thought to decrease excitatory neurotransmission. Gaba-pentin typically is administered orally at a dosage of 10 mg/kg every eight hours in dogs. There are anecdotal reports of gabapentin use in cats with seizures (5-10 mg/kg PO, q8-12 hours).

Clinical efficacy reports in refractory epileptic dogs treated with gabapentin as an add-on therapy indicate that fewer than half of such dogs are responders (i.e., experience a 50 percent or more reduction in seizures after adding gabapentin). However, gabapentin is the least effective of the new anticonvulsant drugs. Side effects typically are mild, and include minor sedation and pelvic limb ataxia.

Gabapentin is available in generic form at a much lower price than the trade-name formulation.

Felbamate is suspected to exert its anticonvulsant effects via potentiating GABA-mediated neuronal inhibition, mitigating NMDA-mediated neuronal excitation and inhibiting voltage-gated neuronal sodium and calcium channels.

Felbamate typically is dosed initially at 15 mg/kg orally every eight hours. There is limited published information regarding its efficacy, but it is generally believed to be an effective anticonvulsant add-on agent. Side effects are uncommon, but hepatotoxicity (usually with concurrent high phenobarbital blood levels), reversible blood dyscrasias and keratoconjunctivitis sicca have been reported with felbamate use in dogs. There is no information on its use in cats.

Considering the hepatic and blood dyscrasia issues associated with felba-mate use in humans and dogs (uncommon as they may be), it is unlikely that there will be much impetus to pursue research into feline felbamate use. There is no generic formulation available for felbamate.

Levitiracetam has been shown to have a unique intracellular binding site, a synaptic vesicle protein (SV2A), the affinity of binding to which appears to be correlated with the drug's anticonvulsant potency. Binding to SV2A affects neurotransmission via interactions between synaptotagmin and calcium ions, but the precise biochemical pathways remain undetermined.

Levitiracetam is an attractive anticonvulsant option due to its lack of side effects and favorable pharmacokinetic profile (e.g., no hepatic metabolism, 100 percent oral bioavailability, no drug-drug interactions). There is limited published information regarding its efficacy as an add-on anticonvulsant in dogs, but so far it is favorable. The dose usually used is 20 mg/kg orally every eight hours. A lower-cost, generic form of oral levitiracetam is available.

Zonisamide has proven to be an effective add-on anticonvulsant drug in dogs, with few side effects. There are multiple proposed mechanisms of action for zonisamide, including blockage of T-type calcium and voltage-gated sodium channels in the brain, facilitating dopaminergic and serotonergic neurotransmission, free-radical scavenging, enhancing GABA activity and decreasing glutamate-mediated processes.

Dogs concurrently receiving pheno-barbital therapy tend to require a higher zonisamide dose (10 mg/kg, q 12 hours) than dogs not receiving phenobarbital (5 mg/kg, q 12 hours). The BID dosing schedule for zonisamide is an advantage over the other new anti-epileptic drugs for many dog owners. It is available in the generic form.

As sole drug therapy

There are a number of reports in human medical literature supporting the use of some of these new anticonvulsant drugs as sole therapy. Because they have minimal side effects, they may offer an advantage over more standard drugs used in dogs. And, as the price decreases for generic versions, there will be more opportunities to use these newer agents as standard therapy, especially in small-breed dogs.

Anecdotally, felbamate can be used as a sole anticonvulsant drug. In most cases, it is used to avoid the side effects of phenobarbital or potassium bromide. Such cases include the management of disorders in which the underlying disease and its treatment may result in worsening clinical signs with the addition of standard anticonvulsant drugs (e.g., obtunded brain tumor and GME dogs receiving prednisone).

In addition, dogs with suspected idiopathic epilepsy have been treated with zonisamide as a sole anticonvulsant drug. It appears to perform well as a sole anticonvulsant drug for canine idiopathic epilepsy.

New feline anticonvulsant drugs

Until recently, the only anticonvulsant drug known to be safe and effective for feline use was phenobarbital. The use of gabapentin for seizures in cats remains anecdotal, with unproven efficacy. Due to the length of time that such anecdotal use has been discussed in the veterinary literature (with no reports of serious side effects), and the known safety of the drug in other species (i.e., humans, dogs), it is likely to be a safe drug in cats.

Levitiracetam has been used as an add-on (to phenobarbital) oral anticonvulsant drug in a few cats with suspected refractory idiopathic epilepsy. It was found to be an effective add-on anticonvulsant, and serum levitiracetam levels are maintained within the therapeutic range reported for people (5-45 ug/mL) using a 20 mg/kg every 8 hours dosing regimen. Side effects are limited to transient (one to two weeks) lethargy and inappetence; these resolved without adjusting drug dosage.

Levitiracetam can be used as second-line anticonvulsant drug choice for cats poorly controlled with phenobarbital alone.

Emergency seizure management

The current standard of care for treating dogs with cluster seizures or *status epilepticus* is to administer highly sedative drugs to halt seizure activity. As diazepam often fails in these animals, the induction of a light plane of anesthesia using barbiturates or propofol often is required.

In addition to posing some risk, it may be difficult or impossible to add additional maintenance anticonvulsant drugs to the treatment protocol during this time period.

Both intravenous levitiracetam and intra-rectal zonisamide hold potential as useful emergency anticonvulsant treatment options for dogs.

A commercial form of intravenous levetiracetam was recently introduced. A single-dose pharmacokinetic study with this drug formulation in normal dogs, using an intravenous bolus dose of 60 mg/kg over two minutes, showed no apparent side effects and all dogs reached and maintained plasma levitiracetam concentrations within or exceeding the therapeutic range reported for humans for the entire eight-hour evaluation period.

A prospective clinical evaluation of intravenous levitiracetam use in dogs with cluster seizures and status epilepticus is under way.

Newer versions

Recent insights into the mechanisms of action of two of the new anticonvulsant drugs (gabapentin and levitiracetam) have generated developments of the next generation drugs with increased anticonvulsant potency.

The successor to gabapentin is pregabalin, which has greater affinity for the voltage-gated calcium channels than its predecessor. There are two successors to levitiracetam — brivaracetam and seletracetam — both of which have greater affinity for SV2A than levitiracetam.

Because of the problems of hepatotoxicity and blood dyscrasias occasionally associated with felbamate use in people, a new derivative of the drug, fluorofelbamate, has been developed. The substitution of fluorine for hydrogen in a critical place in the molecule is believed to prevent the formation of the toxic metabolite responsible for the reported side effects.

All of these drugs appear to have greater anticonvulsant activity in experimental rodent models than their predecessors. Pregabalin also has shown greater anticonvulsant efficacy than gabapentin in people. Brivaracetam, seletracetam and fluorofelbamate are in clinical trials. Pregabalin is commercially available, but the appropriate dose regimen for oral pregabalin in dogs is still unknown.

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