From Gold Beads to Keppra: Update on Anticonvulsant Therapy

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The search for effective antiepileptic drugs began over 2000 years ago. Over the centuries, both natural and synthetic substances have been administered with varying degrees of success and the search for a "**cure**" continues and parallels research into the basic mechanisms of epileptic brain discharges. The first known attempt at a scientific explanation for epilepsy appeared in the book *On the Sacred Disease*, written about 400 BC. At that time those who suffered from epileptic seizures were believed to be possessed by evil spirits or gods, and the treatment was to be rendered through religious, occult, or magical powers. As time passed two treatment approaches for epilepsy evolved: the natural approach and the supernatural approach. Unfortunately, the ineffectiveness of most natural therapies such as dietary changes allowed the idea of possession to prevail, making exorcism a popular remedy in those days. In what is considered the modern era of anticonvulsant drug development, clinical seizures could be produced in laboratory animals by a variety of procedures and further development of animal models paralleled and was dependent on developing new drugs for the treatment of epilepsy. As early as 1857 Locock administered bromides to treat hysterical seizures in women and phenobarbital was the first synthetic chemical agent used in the management of epilepsy in people. It has only been over the last fifty years that information on basic mechanisms of epilepsy, pharmacology of antiepileptic medication and experimental models of epilepsy have helped pushed the development of newer drugs for seizure control.

Both dogs and cats may demonstrate seizure activity and the frequency has been estimated at 0.5 to 5.7% and 0.5 to 1% respectively. The pathogenesis of recurrent seizures activity is complex and probably involves genetic, intrinsic biochemical neuronal changes and environmental factors. The basic mechanism thought to be responsible for recurrent seizures activity is an imbalance in the excitatory and inhibitor processes of neuronal neurotransmission. Seizures develop when the balance shifts towards excessive neuronal excitation. Recent research and the development of new anticonvulsants has focused on the role of glutamate, its receptor complex, N-methyl-D-aspartate, and the activity of Gamma-aminobutyric acid, the main inhibitory neurotransmitter in the brain, and there associated ion channels. As a result of this research antiepileptic drugs can be classified into three broad mechanistic categories: enhancement of inhibitory processes, reduction in excitatory neuronal activity and modulation of membrane conductance. The main inhibitor neurotransmitter in the brain is Gamma amino-butyric acid and these receptors are coupled to the chloride channel. An increased chloride channel opening results in a chloride-mediated hyperpolarization of the neuronal membrane. This hyperpolarized state makes it difficult for a paroxysmal depolarization shift to occur which is the hallmark of a seizure discharge. Examples of anticonvulsants that work at this site include benzodiazepines which increase the frequency, while the barbiturates increase the duration of chloride channel openings. Glutamate is the major excitatory neurotransmitter in the brain. The release of glutamate causes excitatory post-synaptic potentials via activation of glutaminergic receptors such as the N-methyl-D-aspartic (NMDA). Examples of anticonvulsants that work at reducing glutamate mediated excitation include felbamate, phenobartibal, gabapentin and topiramate. The last category of action is that of reducing the prolonged calcium-dependent neuronal depolarization associated with the paroxysmal depolarization shift. Examples of anticonvulsants that utilize this mechanism to inhibit seizures include phenobarbital, gabapentin and zonisamide.

FELBAMATE

Felbamate is a dicarbamate anticonvulsant that was developed in the process of modifying a structurally similar antianxiety agent, meprobamate. Felbamate was approved in the United States in 1993 for

use in human epileptics with partial seizures and is effective in several seizure models, including both generalized and partial seizures in animal studies. Pharmacokinetic studies in dogs have determined the half-life of the drug to be 5 to 8 hours and a large majority of felbamate is excreted renally unchanged, with a small portion excreted in the feces after hepatic metabolism in dogs. The recommended starting dose in epileptic dogs is 15 to 20 mg/kg TID and the dose can be increased up to 65 mg/kg as needed to control seizure activity. In the initial drug studies, no toxicity was observed in dogs receiving daily dosages ranging from 30 mg./kg to 300 mg/kg.[7] However in humans receiving felbamate a limited number of aplastic anemia cases and hepatotoxicity have been reported. This potentially fatal side effect has not been reported in dogs. Limited side effects that have been reported in dogs receiving felbamate and it is recommended that a complete serum chemistry panels be monitored every 4 to 6 months during treatment to assess for liver toxicity. Felbamate is generally used in combination with phenobarbital and or potassium bromide, however there is a report of the use of felbamate monotherapy in dogs with partial seizures. The main disadvantages of using felbamate in dogs include three times daily dosing and the cost. The approximate monthly cost to treat a 25 kg dog with felbamate is $150.

GABAPENTIN

Since 1994 Gabapentin has been approved in the United States for treatment of partial seizures with or without generalization in human patients. The pharmacokinetic studies in people suggest that the drug is eliminated entirely by the kidneys; however, gabapentin does undergo partial hepatic metabolism in dogs. It is unknown whether the metabolite N-methylgabapentin has any antiepileptic properties in animal and the elimination half-life in dogs is 2-4 hours. These results would suggest that the serum steady state concentration may be difficult to maintain without frequent administration. The recommended starting dosages in dogs is 30-60 mg/kg/day divided every 6-8 hours and the only side effect that has been reported is sedation. There have been no clinical studies evaluating the efficacy of gabapentin for canine epilepsy, but anecdotal reports suggest that it may be beneficial in the treatment of both partial and generalized seizures in dogs. Gabapentin has other potential uses in animal and in a recent animal study demonstrated the ability of relieving neuropathic pain in a peripheral neuropathy model. Similar to felbamate, the main disadvantages of gabapentin is the frequency of administration and the cost. The approximate monthly cost to treat a 25 kg dog is $140.

ZONISAMIDE

Zonisamide is a sulfonamide derived antiepileptic drug that was approved by the FDA in 2000 as adjunctive treatment for partial onset seizures in humans. Zonisamide appears to have a favorable pharmacokinetic profile in dogs with rapid and complete absorption after oral administration. Zonisamide has a long half-life (15 hours) which would allow for twice daily administration. Eighty percent of the drug is reported to be excreted unchanged in the urine although some hepatic metabolism occurs. Zonisamide is not reported to cause induction of liver enzymes like other anticonvulsants and this may be of significance when phenobarbital and zonisamide are used in combination, as phenobarbital is known to induce hepatic enzymes which are responsible for the metabolism of zonisamide. The recommended starting dosages in dogs is 5 to 10 mg/kg every 12 hours. Serum concentrations have been measured in dogs and are comparable to the therapeutic range that has been established for humans, 20-30 µg/ml, treated with zonisamide. Toxicity studies suggest that chronic administration appears to be safe in dogs. Side effects reported in dogs appear to be mild and include transient sedation, ataxia and loss of appetite. In a recent study fifty-eight percent of the dogs with poorly controlled idiopathic epilepsy were administered oral zonisamide at a dosage adequate to achieve serum drug concentrations of 10 to 40 µg/mL and responded favorably with a reduction in seizures frequency. The limiting factor with the use of zonisamide in dogs appears to be the expense as the approximately monthly cost to treat a 25 kg dog is $180.

TOPIRAMATE

Topiramate is a sulfamate-substituted monosaccharide anticonvulsant that was found to be effective against both generalized and partial seizure activity in both humans and animal studies. Topiramate is unique in that it is reported to have four different mechanisms of action in reducing seizure activity. In beagles topiramate was shown to have rapid absorption following oral administration of either single or multiple dosages. The half-life of topiramate is reported to be between 2.0 to 3.8 hours after multiple doses and the pharmacokinetics suggest that greater than 90% of the drug is eliminated unchanged via the kidneys. There is also no evidence that suggest autoinduction or inhibition of enzymes that metabolize topiramate occurs and the recommended starting dosage is 5 to 10 mg/kg orally twice a day. It is recommended to start at the lower dosage to prevent the possible adverse effects that have been reported with topiramate which include gastrointestinal upset, irritability, ataxia and one case of topiramate-induced urolithiasis in a person. However no long-term toxicity studies for topiramate have been completed in dogs. The expense of topiramate is similar to both felbamate and zonisamide.

LEVETIRACETAM

Levetiracetam is one of the latest antiepileptic drugs licensed in adult patients with partial seizures with or without secondary generalization that are refractory to established first-line drugs. Levetiracetam is a chiral molecule with one asymmetric carbon atom whose anticonvulsant activity is highly enantioselective. In addition Levetiracetam is reported to have a different mechanism of action when compared to existing antiepileptic drugs, although the actual mechanism of action still remains unknown. The pharmacokinetic and safety studies in beagle dogs suggest that levetiracetam has a favorable profile. Levetiracetam has rapid absorption after oral administration and over 80% of the drug is excreted renally in dogs, with minimal hepatic metabolism and excretion in the bile. The half-life in dogs is reported to be 3.3 hours, which would require frequent administration. The recommended dose is 20 mg/kg given every 8 hours. Preliminary toxicity studies suggest that chronic oral administration of levetiracetam is safe in dogs, however a recent report described the first case of polyneuropathy induced by levetiracetam in a person[18]. There is currently has a study underway evaluating levetiracetam as an add-on treatment for dogs refractory to phenobarbital and potassium bromide at the Veterinary Teaching Hospital at North Caroline State University but the results are not available yet. As is the case with all of the newer antiepileptic drugs, the main factor limiting its use is expense and the approximate monthly cost to treat a 25 kg dog with levetiracetam is $200.

STIRIPENTOL

Stiripentol is a novel anticonvulsant that is structurally unrelated to any other currently available antiepileptic drug and has been reported to be effective in severe myoclonic epilepsy of infants. Stiripentol has been under investigation since the 1970s when it was first synthesized and although its precise mechanism of action remains unknown, one study it demonstrated that stiripentol increased gaba-aminobutyric acid (GABA) levels in the brain. While another study suggested that stiripentol induces increased GABA concentration in two independent neurochemical mechanisms, first via inhibition of synaptosomal uptake of GABA and secondly inhibition of GABA transaminase as stiripentol shows no affinity for either $GABA_A$ or $GABA_B$ receptors. No pharmacokinetic studies or dose recommendation are available for the dog at this time.

ELB138

A new antiepileptic and anxiolytic drug, ELB138, has been evaluated in a recent clinical study in 29 dogs with newly diagnosed or chronic idiopathic epilepsy. The exact mechanism of action of ELB138 is not yet fully understood. One possible mechanism of action is thought to be related to a very low affinity

for the benzodiazepine binding site of the $GABA_A$ receptor within the brain, as the pharmacological activity of ELB138 can be counteracted by flumazenil. ELB138 was also found to block voltage-activated Ca^{2+} channels in a dose dependent manner, which may contribute to the anticonvulsant activity. The pharmacokinetic for ELB138 have been previously reported and are favorable in the dog. The effective dose of ELB 138 is reported to be 20 mg/kg every 12 hours based on initial studies. While the pilot study suggested ELB138 has a potent anticonvulsant effect in dogs with idiopathic epilepsy additional multicentre blinded studies are needed to confirm these findings. The Reported side effects in dogs treated with ELB138 were rare, and consisted mostly of transient polyphagia.

VAGAL NERVE STIMULATION

Researchers in the 1930's initially demonstrated that stimulation of the cervical vagus nerve in cats resulted in changes to the electroencephalographic pattern. In 1985, Zabara hypothesized that epileptic discharges could be interrupted or prevented by stimulating the vagus nerve and his theory was subsequently validated in animal studies. As a result of this work the Neurocybernetic Prosthesis, an implantable pacemaker device that delivers a repetitive stimulus to the left cervical vagus nerve was developed and approved in humans as an adjunctive treatment for partial seizures. In 1999 the first reported use of vagal nerve stimulation in naturally occurring seizures in dogs was reported, when ocular compression was used as a means to increase vagal tone in epileptic dogs with limited success. A recently study evaluated electrical vagal nerve stimulation as a treatment for refractory epilepsy in 10 dogs. The results showed no significant difference in seizure frequency, duration, or severity as detected between the overall 13-week treatment and control periods. However during the final 4 weeks of the treatment period, a significant decrease in mean seizure frequency was detected, compared with the control period. Some minor complications were reported and included a transient bradycardia, asystole and apnea during the intraoperative testing. Subcutaneous migration of the generator, seroma formation and a transient Horner's syndrome were reported in the postoperative period. The results of this study suggest that vagal nerve stimulation is a potentially safe procedure in dogs and appears to be efficacious in certain dogs and maybe an alternative form of seizure control when treatment with antiepileptic medications has failed.

KETOGENIC DIET

The ketogenic diet is a special diet used to treat seizures in young children and some adults. It was initially studied in the 1920's as a treatment option for those with intractable epilepsy. Recently there has been a resurgence of interest in the Ketogenic diet for seizure control in animals. The ketogenic diet is a stringent, mathematically calculated diet high in fat and low in protein and carbohydrates, in addition, fluids are limited, which helps contribute to the diet's success in people when followed conscientiously. Supposedly the high concentration of ketones in the body controls the frequency and severity of seizures, although the exact biochemical mechanism by which the Ketogenic Diet works is still unknown. One thought is that ketosis, dehydration and acidosis each appear to play a role in altering in the acid-base balance, water and electrolyte distribution, lipid concentration and brain energy reserves. Ketosis may also have a central action on the brain that results in better seizure control. Several studies have looked at different diets and the development of ketosis in dogs. A recent multi-institutional, prospective, double masked, placebo controlled study found no difference in seizure frequency between dogs on the ketogenic food and the dogs on control food despite the differences in serum concentrations of beta-hydroxybutyrate, the main metabolite of the ketogenic diet. The authors of the study did noted that the number of dogs (22) may have been to small to show a significant differences between the two treatment groups. Additional studies are needed to demonstrate the benefits of the ketogenic diet.

GOLD BEADS

In the early 1970's the first gold bead implantation were done by Dr. Grady Young in the United States. Dr. Young used the gold beads at acupuncture points to cause long-term stimulation of the selected points. In 1975 Dr. Terry Durkes started doing clinical research in gold bead usage and initially treated seizure disorders and hip dysplasia with bead implantation. It has been found that conditions that respond to gold are usually chronic, have excessive negative charge, and have localized alkalosis. Gold bead implantation has also been reported to work well in the treatment of both congenital and idiopathic seizures. In a clinical trial involving 40 dogs with idiopathic seizures, 50% could be taken off of all medication after receiving gold bead implantations, without the risk of further seizure episodes unless the animals were stressed. Another 25% were able to function on a greatly reduced level of medications and there was a 25% failure rate. The basic points that are used for gold bead implantations to treat convulsions are as follows: BL-4, BL-6, GB-14, GB-20 and GV-20. The gold beads are placed just under the skin and on the acupuncture points. The object is to have the electrical values in the normal range if the beads have been implanted correctly. The results with gold bead implantation are very encouraging, however a multi-institutional, prospective, double blinded placebo controlled study is needed to show a significant difference between the two treatment groups. Reported complications from gold bead implants are severe infection at the implantation sites secondary to poor site preparation.