Clinical Studies

Evaluation of the Chinese Herbal Formula *Di Tan Tang* as an Oral Add-On Therapy for Dogs with Presumptive Refractory Idiopathic Epilepsy: An Open-Label Investigation in 8 Dogs

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ABSTRACT

Idiopathic (genetic) epilepsy is a common neurologic disorder of dogs and 25%-30% of these dogs are refractory to antiseizure drug therapy. The purpose of this open-label clinical trial was to evaluate the potential efficacy and tolerability of a traditional Chinese herbal formula *Di Tan Tang* as an add-on therapy for dogs with refractory presumptive idiopathic epilepsy. Eight dogs with refractory presumptive idiopathic epilepsy were evaluated for seizure frequency 3 months prior to and 3 months after instituting oral *Di Tan Tang* therapy (0.5g/10lbs body weight, q 12 hrs) using a prospective open-label, non-comparative clinical trial design. The overall mean reduction in seizure frequency after treatment with *Di Tan Tang* for the 8 dogs was significant (p=0.035) at 27%, with 2 dogs qualifying as responders (≥50% reduction in seizure frequency). One dog experienced mild sedation after starting *Di Tan Tang*; no other adverse effects were recorded for the remaining dogs. The results of this preliminary investigation suggest that *Di Tan Tang* may be a useful adjunctive treatment option for dogs with refractory epilepsy. Further clinical investigation into the potential use of *Di Tan Tang* in canine refractory epilepsy is warranted.

Key words: epilepsy, seizures, refractory, dogs, Chinese herbal medicine, *Di Tan Tang*

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ABREVIATIONS

CBC	Complete blood count
GABA	Gama-aminobutyric acid
IE	Idiopathic epilepsy
TCM	Traditional Chinese medicine
TCVM	Traditional Chinese veterinary medicine

Idiopathic epilepsy (IE), also termed genetic epilepsy, is a common neurologic disease affecting dogs, and approximately 25% to 30% of these patients are refractory to standard antiseizure drug therapy.[1-4] Despite the availability of several new antiseizure drugs, there remains a paucity of safe and effective options for seizure reduction in epileptic dogs. Dogs with refractory IE are often faced with suboptimal seizure control, combined with adverse effects (e.g., sedation, polydipsia/polyuria, polyphagia, liver damage) of multiple antiseizure drugs.[1-5] There is continued interest by the veterinary community and pet-owning public in the use of complementary treatment options for canine epilepsy, including acupuncture, dietary manipulations and herbal therapy.[6-9] The Chinese herbal formulation *Di Tan Tang*[a] has purportedly been a successful anticonvulsant option for dogs with seizure disorders.[9] The individual herbal components and actions of *Di Tan Tang* are provided in Table 1.

Experimental rodent studies and limited human clinical trials suggest some level of efficacy of Chinese herbal treatments, including those found in *Di Tan Tang,* in controlling seizure activity.[10-13] Despite its popularity among veterinary herbalists, there are no published clinical studies to support the use of *Di Tan Tang* as an antiseizure treatment option in dogs, and the reports of success remain entirely anecdotal. The purpose of this pilot clinical trial was to investigate the efficacy of *Di Tan*

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Tang as an add-on oral treatment for dogs with presumptive refractory IE. To the authors' knowledge, this is the first clinical trial investigating the use of a Chinese herbal formula for treatment of canine idiopathic epilepsy.

MATERIALS AND METHODS

The study was conducted as a prospective open-label, non-comparative clinical trial (i.e., owners and investigators were not blinded as to treatments administered to each dog, and the herbal formula was not compared against a placebo or other treatment arm). The Institutional Animal Care and Use Committee at Cornell University approved the study, and owners of all dogs enrolled in the study provided written consent.

Dogs with a presumptive diagnosis of refractory idiopathic epilepsy were eligible for inclusion into the study. Diagnosis of idiopathic epilepsy was based on each patient satisfying the following criteria: 1) onset of generalized seizure activity between 1 and 5 years of age, 2) intermittent seizures for more than 6 months, 3) normal neurologic examination during the inter-ictal period, and 4) results of hematologic analysis (i.e. CBC and serum biochemical analysis) within the respective reference ranges (except for those abnormalities attributable to anti-seizure medications). Dogs with focal (partial) seizures were also eligible for study inclusion, provided they also experienced generalized seizures. Dogs whose seizure history began after 5 years of age were considered, if they met the other stated criteria and had normal magnetic resonance imaging of the brain. The diagnosis of refractory epilepsy was based on dogs having an average of 2 or more seizures per month, despite receiving appropriate doses of at least two antiseizure drugs. Steady-state concentrations of at least one of the drugs within the therapeutic range was also a requirement for study inclusion. Dogs with subtherapeutic levels of additional drugs were eligible for inclusion, providing they were experiencing untoward side effects of drug therapy, precluding dosage increases.

Only dogs whose owners maintained accurate seizure logs, documenting seizure frequency, were eligible for inclusion. Each dog required a minimum seizure history of 3 months with steady-state levels of all antiseizure drugs (based on drug elimination half-lives) prior to entering the study, with at least 6 total seizures occurring during that time period. In cases of cluster seizures, in which the number of seizures was not clearly documented, the cluster was counted as one seizure event. As part of inclusion criteria, no changes in drugs or other anti-seizure treatments were allowed for the 3-month pre-treatment period. In order to remain in the study, no changes in drugs or any other anti-seizure interventions were allowed for the 3-month post-*Di Tan Tang* evaluation period. An approximate oral *Di Tan Tang* dose (commercially available product[a] of 0.5g/10lbs body weight, every 12 hrs was administered to each dog for a period of 3 months. Adverse effects attributable to *Di Tan Tang* administration were recorded. A CBC and serum chemistry were evaluated prior to and following the *Di Tan Tang* trial. Individual patient success was defined as a minimum of 50% seizure frequency reduction (i.e., responder) when comparing the 3-month herbal treatment period to the preceding 3-month time period (based on owner's seizure logs). Seizure frequency was compared between the *Di Tan Tang* treatment period and the pre-treatment period using a non-parametric Wilcoxon signed rank test for paired data. The statistical significance was set at $p \leq 0.05$. It was estimated that, for comparisons of paired data, a sample size of 11 dogs was desired to achieve an 80% power to reject the null hypothesis, when the difference is at least as large as the standard deviation of the observed differences. Statistical analysis was performed using a commercial software[b].

RESULTS

Thirteen dogs met the criteria for the study, and 8 completed the study. Of the five dogs that failed to complete the study, 2 dogs required additional drug therapy because of uncontrolled seizure activity and 3

Table 1: Ingredients of the Chinese herbal medicine *Di Tan Tang*[a] and their actions

***Pin Yin* Name**	**English Name**	**Actions[9]**
Zhu Ru	Bambusa	Transforms Phlegm
Fu Ling	Poria	Drains Damp
Shi Jue Ming	Haliotis	Clears Liver Heat
Chen Pi	Citrus	Moves *Qi*, transforms Phlegm
Gou Teng	Uncaria	Extinguishes Internal Wind, clears Liver Heat
Hai Zao	Sargassum	Transforms Phlegm, clears Heat
Kun Bu	Laminaria	Transforms Phlegm, drains Damp
Shi Chang Pu	Acorus	Opens orifices, eliminates Damp
Zhi Shi	Aurantium	Moves *Qi*
Tian Nan Xing	Arisaema	Transforms Phlegm
Dang Shen	Codonopsis	Tonifies *Qi*
Gan Cao	Licorice	Harmonizes
Gan Jiang	Zingiberis	Harmonizes

dogs either died (1 dog) or were euthanized (2 dogs) due to uncontrollable seizures. Seizure history prior to study enrollment for the 8 dogs ranged from 8 months to 11 years (mean=3.71 yrs; median=2.5 yrs). The mean and median numbers of drugs these dogs were receiving at the time of trial initiation were 3.6 and 3.5, respectively. Three dogs (dog 2, 3, and 6, Table 2) were also receiving a prescription diet for seizures[b]. Table 2 provides a summary of signalment and history data, anti-seizure drug therapy, and pre-and post-*Di Tan Tang* seizure numbers for the 8 dogs that completed the trial.

Overall mean and median seizure reduction after treatment with *Di Tan Tang* was 26.9% (SD=25.3%) and 29.5%, respectively, and this was statistically significant (p=0.035). Two of the 8 dogs (25%) were considered responders (dogs 3 and 6, Table 2), having experienced more than 50% seizure reduction after instituting *Di Tan Tang* therapy. One dog (dog 5, Table 2) experienced mild sedation during the 3-month *Di Tan Tang* treatment period, and this resolved after discontinuing therapy. No CBC or serum chemistry abnormalities attributable to *Di Tan Tang* therapy were identified in any dog.

DISCUSSION

The results of this open-label clinical trial suggest that the Chinese herbal medicine formula, *Di Tan Tang*, may possess some measurable antiseizure activity in dogs suffering from refractory IE. It is important, however, to recognize the limits of this type of study, especially in comparison with a randomized, placebo-controlled clinical investigation. Open-label clinical trials are commonly performed in veterinary medicine for several reasons. These investigations are much less costly and time-consuming than randomized placebo-controlled studies. In addition, owners of dogs with severe medical conditions (such as refractory IE) are generally reticent to enroll their pets into clinical trials that will entail a prolonged treatment period with a placebo. These factors are likely at least part of the reason that there are very few randomized, placebo-controlled clinical trials regarding treatment of refractory canine epilepsy published in veterinary medicine.[14] Nonetheless, the "gold standard" for evaluating a therapeutic intervention remains randomized, placebo-controlled studies.

The results of the current investigation should therefore be interpreted as preliminary findings or pre-clinical evidence, as both the extent of seizure reduction and percentage of responders in this investigation are consistent with reported levels of placebo effect in canine epilepsy.[15] Preliminary findings are an important aspect of evidence-based medicine, as they can help guide investigators in decisions regarding whether to pursue more in-depth and costly investigations (such as a randomized, placebo-controlled trial) into specific treatment options. In addition to cost concerns, there is an ethical concern with respect to conducting placebo-controlled studies with refractory epileptic patients. In refractory human epileptics, there is a potential risk of increased mortality for those patients in the placebo arm of the research trial.[16,17] Evaluating a potential treatment modality in a placebo-controlled trial without any preliminary evidence of efficacy may compound health risks to the patient. Another aspect of this study to consider when interpreting the results is the dropout rate. The fact that five dogs failed to complete the trial due to uncontrollable seizure activity reflects the severity of refractory idiopathic epilepsy. The dropout rate for this investigation also suggests that the potential efficacy of *Di Tan Tang* for refractory epileptics may be more limited than suggested by the data.

From a TCVM standpoint, Chinese herbal formulas for dogs with seizure disorders are typically chosen based on a pattern diagnosis. Although most dogs with idiopathic/genetic epilepsy are likely afflicted with a Kidney *Jing* Deficiency, there are multiple possible TCVM patterns that can be associated with epilepsy. These include one excess pattern (Liver *Qi* Stagnation with Internal Profusion of Phlegm-Fire) and several deficiency patterns. Prolonged disease states may lead to Liver or Kidney *Yin* Deficiency, Liver Blood Deficiency or combinations of these patterns. There are several Chinese herbal formulas available for treating dogs with seizures, each directed at specific patterns. Some other examples of Chinese herbal formulas for seizure management include *Ding Xian Wan*, *Tian Ma Gou Teng*, *Yang Yin Xi Feng* and *Bu Xue Xi Feng*. In dogs with mixed pattern diagnoses, more than one such Chinese herbal formula may be indicated.[18] In the context of performing a clinical trial, it would not be feasible to adhere to TCVM pattern diagnoses and thereby either treat with multiple different formulas or restrict patients to one specific pattern diagnosis. From a conventional medical standpoint, *Di Tan Tang* contains numerous plant species that have been demonstrated to exhibit anti-seizure activity, so it can be administered to patients with seizure disorders without regard to a TCVM pattern diagnosis. Although the conventional medical diagnosis approach more easily allows for a clinical trial to be performed for an individual Chinese herbal formula, the possibility exists that more effective seizure control may have been achievable if additional Chinese herbal formulas could have been instituted, based on TCVM pattern diagnoses.

In recent years, extensive research has been published concerning the molecular basis of action for chemical components of individual herbs. Most of this research was conducted using rodent models and cell cultures. Herbal molecules that have been associated with anti-seizure effects are generally categorized as flavonoids, coumarins, phenylpropanoids and terpenoids. Specific anti-seizure mechanisms of actions have been elucidated for several of the herbal components of *Di Tan Tang*.

Naringenin (4',5,7-trihydroxyflavanone) is a flavonoid found in citrus fruits (*Chen Pi*, *Zhi Shi*) that has exhibited anti-seizure effects in mouse seizure models. Potential modes of action of naringenin include inhibition of the mTOR pathway, decreased production of microglial-derived pro-inflammatory cytokines, reduced

lipid peroxidation of cell membranes and reduction of hippocampal neuronal cell damage and death.[19,20] Hesperetin (3',5,7-trihydroxy-4'-methoxyflavanone) is another flavonoid compound found in citrus fruits that has exhibited neuroprotective and anti-seizure effects in a mouse model of temporal lobe epilepsy; hesperetin was demonstrated to inhibit expression of microglial-derived pro-inflammatory molecules and attenuate granule cell dispersion in the hippocampus.[21]

Rhyncophylline is an oxindole alkaloid derived from *Gou Teng* (*Uncaria*) that has been shown to protect neurons against NMDA-mediated excitotoxicity in rat seizure models.[22,23] Fucosterol is a sterol found in *Hai Zao* (*Sargassum*) that has demonstrated both neuroprotective and anti-seizure effects in a mouse seizure model; these effects may be attributable to increases in brain neurotransmitters, such as serotonin, epinephrine and 5-hydroxyindoleacetic acid.[24] Alpha (α)-asarone (1-propenyl-2,4,5-methoxybenzol) is a phenylpropanoid compound derived from *Shi Chang Pu* (*Acorus*). Alpha (α)-asarone is believed to exert its anti-seizure activity via enhancing GABA-ergic neuronal inhibition.[25,26]

Table 2: Summary of pre-and post-*Di Tan Tang*[a] seizure numbers in 8 dogs

Dog	Signalment	Epilepsy Duration	Concurrent Use of Anti-Seizure Drug Therapy	Seizures Before *Di Tan Tang*	Seizures After *Di Tan Tang*	Seizure Frequency Change
1	7 yr,7 mo Shih Tzu MC	3 yrs	Zonisamide Potassium bromide Pregabalin	7	6	-14%
2*	9 yr, 3 mo Dachshund MC	3 yrs	Phenobarbital Potassium bromide Zonisamide Levetiracetam Pregabalin Felbamate	25	24	-4.0%
3*	7 yr, 7 mo Cavalier King Charles Spaniel FS	6.5 yrs	Phenobarbital Potassium bromide Levetiracetam Pregabalin	12	5	-58%
4	5 yr, 7 mo Border Collie MC	8 mos	Zonisamide Levetiracetam	12	7	-42%
5	14 yr, 9 mo American Eskimo MC	11 yrs	Phenobarbital Zonisamide	22	13	-41%
6*	5 yr, 5 mo Shetland Sheepdog MC	2 yrs	Phenobarbital Potassium bromide Zonisamide Levetiracetam Topiramate	19	9	-52%
7	2 yr Boxer MI	1.5 yrs	Phenobarbital Zonisamide Levetiracetam	11	9	-18%
8	4 yr Siberian Husky MC	2 yrs	Phenobarbital Potassium bromide Zonisamide Levetiracetam	7	8	+14%

MC=male castrated; MI=male intact; FS=female spayed; yr=year; mo=month
*Also received prescription diet for seizures

Glycyrrhizin is a triterpene compound derived from *Gan Cao* (*Glycyrrhiza*) that has exhibited several neuroprotective effects. In addition to preventing excitotoxic damage in primary cell cultures, glycyrrhizin demonstrated antioxidant and anti-inflammatory effects in a rat status epilepticus model.[27] In one mouse seizure model investigation, a hydroethanolic extract of *Gan Jiang* (*Zingiber*) displayed anti-seizure effects. These effects were suspected to be mediated via interactions with excitatory and inhibitory neurotransmitter systems, as well as inhibition of oxidative stress and calcium channels.[28]

Although the use of individual Chinese herbs and herbal formulas for treating epilepsy is generally considered a non-pharmacological treatment approach, such a categorization is somewhat tenuous. A large proportion of modern pharmaceuticals are plant derived. The identification and potential modulation of biologically active molecular compounds in plants that target specific disease processes is a central theme of drug discovery. In addition to the compounds evaluated from the individual herbal components of *Di Tan Tang*, numerous other such studies have been conducted for Chinese herbs with anti-seizure activity that are not included in *Di Tan Tang*.[8-11] There is considerable potential for creating new pharmaceutical agents using compounds found in individual plants. There is also a possibility of devising new Chinese herbal medicine formulas that are more effective than the traditional formulas by applying modern evidence of individual herbal efficacy. In other words, modern-day veterinary herbalists have an advantage over the ancient Chinese herbalists in knowing the mechanisms of action and potential efficacy of molecular compounds found in individual herbs.

In both human and canine epilepsy clinical trials, one of the main indicators of success or failure of an antiseizure intervention is the number of responders, with responders being those patients who experienced at least a 50% reduction in seizure frequency after instituting the intervention being evaluated.[1,3,4,14] In our study, only 25% (2 dogs) qualified as responders. However, 2 additional dogs experienced more than 40% reduction in seizure frequency after adding in *Di Tan Tang* to the treatment regimen. Although these two dogs (dogs 4 and 5, Table 2) were not technically treatment successes based on the study criteria, the owners were pleased with the extent of seizure reduction. From a practical clinical viewpoint, *Di Tan Tang* was considered a success in half of the dogs in this study.

In addition to the open-label design of this investigation, study limitations include low case numbers and comparison of prospective seizure data with retrospective seizure data (owners' seizure logs). In addition, due to the nature of refractory canine epilepsy, there was a wide variation in numbers and types of anti-seizure medications being administered to the study participants. Despite the limitations of this study, the results suggest a potential role for *Di Tan Tang* as an adjunctive treatment option for dogs with refractory IE. Another very important finding was that there were no serious adverse events associated with *Di Tan Tang* therapy. Although the results of this clinical trial should be interpreted with caution, they may warrant further investigation into *Di Tan Tang* as an adjunctive treatment for refractory canine idiopathic epilepsy. Future studies into *Di Tan Tang* should include its evaluation in a randomized, placebo-controlled trial as well as investigating the efficacy of this formula when used in combination with other Chinese herbal antiseizure formulas. It would also be of interest to evaluate the efficacy of *Di Tan Tang* in non-refractory canine epileptics. Finally, since the equivalent of a drug half-life is unknown for *Di Tan Tang*, longer term follow-up should be sought in future investigations to determine if seizure reduction improves with more chronic administration. The results of this study, though preliminary, suggest a role for *Di Tan Tang* in the treatment of presumptive canine refractory epilepsy.

Declaration of Interest and Funding

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FOOTNOTES

a. *Di Tan Tang*, Jing Tang Herbal Inc., Reddick, FL, USA
b. R version 3.5.2, The R Foundation for Statistical Computing, Vienna, Austria
c. NC Neurocare™, Purina®, St. Louis, MO, USA

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