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RESEARCH

Effect of clomipramine on the electrocardiogram and serum thyroid concentrations of healthy cats

Kenneth M. Martin, DVM

Veterinary Behavior Consultations, LLC, New Orleans, Louisiana.

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Abstract Clomipramine is a tricyclic antidepressant (TCA) commonly used to treat anxiety related behavioral disorders in companion animals. Tricyclic antidepressants (TCAs) have the potential to cause arrhythmias in humans and companion animals. The effect of the TCAs, clomipramine, and amitriptyline, at therapeutic dosages on cardiac rhythm has been evaluated in dogs. The effect of clomipramine on the cardiac rhythm of cats has not been reported. In Experiment 1, 7 healthy cats were selected to evaluate the effect of clomipramine on their cardiac rhythm using an electrocardiogram. A baseline electrocardiogram was carried out before (Day 0) and repeated (Day 29) after 4 weeks (28 days) of daily clomipramine (10 mg/cat PO) administration. Significant changes in the electrocardiogram were not found after 28 days of daily clomipramine administration. In Experiment 2, 7 healthy cats were enrolled in the study to evaluate the effect of clomipramine administration on the serum thyroid concentrations in cats. Clomipramine (10 mg/cat PO daily) was administered to all cats beginning on Day 1, and continued for 28 days. Serum total thyroxine (T_4), triiodothyronine (T_3), and free thyroxine (fT_4) concentrations were measured before (Day 0) and repeated (Day 29) after 4 weeks (28 days) of daily clomipramine administration. Statistically significant decreases in serum thyroid concentrations (T_4, T_3, and fT_4) were noted between pre and post clomipramine administration. A decrease of 25, 24, and 16% in serum T_4, T_3, and fT_4 concentrations, respectively, may lead to a misdiagnosis of euthyroidism in a subclinical hyperthyroid patient. A longer duration of drug treatment might further suppress thyroid function when used as a single agent, with concomitantly administered drugs, or in conjunction with euthyroid sick syndrome.

Introduction

Pharmacological agents are an integral component in the treatment of animal behavior disorders. These drugs are best used in combination with behavioral and environmental modification, rather than as a sole therapy (Overall, 2001). Clomipramine hydrochloride is a tricyclic antidepressant (TCA) used commonly to treat anxiety-related behavioral disorders in companion animals. Clomipramine is the most serotonin-selective TCA (Boothe, 2001). Clomipramine (Clomicalm, ®Novartis Animal Health, Greensboro, NC) is a Food and Drug Administration-approved product in the United States for the treatment of canine separation anxiety. Although labeled for use in cats only in Australia, the drug has been used commonly in several countries for the treatment of feline anxiety-related disorders that manifest as aggression, fear, compulsion, and inappropriate elimination (urine marking) (Lainesse et al., 2006). All use of the drug in the United States other than the treatment of canine separation anxiety is considered extra label.

Tricyclic antidepressants are well absorbed from oral administration with a bioavailability of 90% in cats

Address for reprint requests and correspondence: Dr. Kenneth Martin, 2330 Somerset Drive, New Orleans, LA 70131.
E-mail: vbcdvm@yahoo.com

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(Lainesse et al., 2006). Clomipramine, like other TCAs, undergoes significant first pass metabolism by the liver using the cytochrome P450 system (Mealey, 2002). Desmethylclomipramine, an active intermediate metabolite of clomipramine, is a more potent inhibitor of norepinephrine and has a longer elimination half life than clomipramine (Martensson et al., 1984). TCAs block the reuptake of norepinephrine and serotonin and are competitive antagonists at the muscarinic acetylcholine, histamine H_1, and α_1 and α_2 adrenergic receptors (Sadock and Sadock, 2001).

The majority of side effects of TCAs are related to the drugs antagonism of cholinergic muscarinic receptors. Anticholinergic side effects are not limited to the heart and may include dry mouth, dry eye, increased intraocular pressure, decreased gastrointestinal activity or constipation, and urinary retention. The sedative effects of TCAs are the result of anticholinergic and antihistaminergic activities. Clomipramine-induced side effects in cats include sedation, decreased appetite, pupil dilation, constipation, and occasional urinary retention (Lainesse et al., 2006).

In humans, orthostatic hypotension is the most common cardiovascular autonomic adverse effect of TCA administration (Sadock and Sadock, 2001). Mechanisms for this effect are not fully understood, although blockade of peripheral alpha adrenergic receptors, stimulation of central alpha adrenergic receptors, and direct non-adrenergic effect have been implicated (Reich et al., 2000). Persistent tachycardia is one of the most common reasons for the drugs discontinuation in young humans (Sadock and Sadock, 2001). Electrocardiogram aberrations of humans treated with TCA include sinus tachycardia and other arrhythmias; prolonged PR, QRS, QT, and QT corrected for heart rate intervals; ST-T segment changes; bundle-branch block; and antiarrhythmic effects (Reich et al., 2000). All TCAs have the potential to cause arrhythmias in companion animals.

Caution is warranted using TCAs in patients with hyperthyroidism or those that are receiving thyroid supplementation because of the increased risk of cardiac rhythm disturbances. Use in combination with sympathomimetic agents may increase the risk of cardiac effects (arrhythmias, hypertension, hyperpyrexia) (Plumb, 2005). The effect of clomipramine and amitriptyline on cardiac rhythm has been evaluated in healthy dogs (Reich et al., 2000). Therapeutic dosages did not induce ECG abnormalities in healthy dogs. Administration of 20 mg of clomipramine/kg to dogs did significantly reduce heart rate, yet changes were benign compared to the dangerous arrhythmias or tachycardia reported in humans (Pouchelon et al., 2000). To the author's knowledge, the effect of clomipramine on the cardiovascular system of cats has not been studied. Cats may be more susceptible to the adverse effects of clomipramine than dogs because TCAs are metabolized through glucuronidation (Overall, 2004). Experiment 1 was designed to evaluate the effect of clomipramine on the electrocardiogram of healthy cats.

Many commonly used drugs may alter thyroid function tests and some can result in hypothyroidism, including sulfonamides, glucocorticoids, phenobarbital, and tricyclic antidepressants (TCAs). Mechanism of TCAs altering thyroid function may include binding iodine (rendering it unavailable), inhibiting thyroid peroxidase (decreasing thyroid hormone production), stimulating deiodinase activity (increasing T_4 degradation), or directly interfering with the hypothalamic-pituitary-thyroid axis (via manipulation of the noradrenergic and serotonergic systems that interact with the hypothalamus, directly increasing or decreasing TRH release) (Sauvage et al., 1998). Clomipramine has been reported to cause significant decreases in serum triiodothyronine (T_3), total thyroxine (T_4), and free thyroxine (fT_4) concentrations in dogs detected on Day 28 of administration (Gulikers and Panciera, 2003). To the author's knowledge, the effect of clomipramine on serum thyroid concentrations has not been reported in cats.

Hyperthyroidism is the most common endocrinopathy of older cats (Gerber et al., 1994). Hyperthyroidism is reported to affect 1 in 300 cats (Mooney, 2001). The incidence is much lower (5%) in cats who are <8 years of age (Meeking, 2005).

A diagnosis of hyperthyroidism is confirmed in most cats with the disease by elevations in serum total T_4 and T_3 concentrations. In approximately 10% of cats with hyperthyroidism, serum total T_4 and T_3 values are within the normal reference range (McLoughlin et al., 1993). Normal serum total T_4 and T_3 concentrations can occur if the cat is mildly hyperthyroid, non-thyroidal illness is present, or if certain drugs have been administered (McLoughlin et al., 1993). Free T_4 is the physiologically active thyroid hormone. The measurement of fT_4 concentrations by modified equilibrium dialysis (MED) produces a more accurate assessment of thyroid function (Schachter et al., 2004). In addition, fT_4 is less likely to be affected by non-thyroidal disease or drug administration than is total T_4 (Kaptein, 1993). However, hyperthyroidism should not be diagnosed solely on the basis of fT_4 because the fT_4 test has an occasional false-positive test result (Peterson et al., 2001).

Experiment 2 was designed to evaluate the effect of clomipramine on the serum thyroid concentrations of healthy cats. Serum total thyroxine (T_4), free thyroxine (fT_4), and triiodothyronine (T_3) levels were evaluated before (Day 0) and repeated (Day 29) after 4 weeks of daily clomipramine administration.

Materials and Methods

Experiments 1 and 2 were conducted simultaneously on the same population of healthy cats.

Animals

Seven healthy, privately owned cats ($N = 7$) were enrolled in the study. Five of the cats were female and 2 of the cats were male. All cats were altered (spayed or neutered). The average age of the cats was 9.28 years, with a