Electrocardiographic assessment of antianxiety medication in dogs and correlation with serum drug concentration

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Objectives—To determine effects of tricyclic antidepressants (TCA) on the ECG of dogs treated for behavioral conditions and to examine correlations between ECG findings and serum concentrations of these medications.

Design—Repeated-measures study.

Animals—39 client-owned dogs with behavioral problems.

Procedure—Two groups of dogs with behavioral problems were evaluated. In group 1 (n = 20), ECG tracings were recorded before starting treatment with TCA and again after treatment for ≥ 1 month. Dogs in group 2 were already on long-term maintenance amounts of antianxiety medication when ECG tracings were recorded and serum concentrations of medications were obtained.

Results—Significant differences were not detected for dogs in group 1 between ECG values measured before and after TCA administration. The ECG values for dogs in group 2 did not differ significantly from the mean of group-1 dogs before receiving medication or from the reference range used at our facility. Duration of the P wave had a significant positive correlation with serum concentrations of clomipramine but significant negative correlation with serum concentrations of amitriptyline. The QT interval corrected for heart rate had a significant negative correlation with serum concentrations of amitriptyline.

Conclusions and Clinical Relevance—Amitriptyline and clomipramine administered at standard dosages apparently do not cause ECG abnormalities in healthy dogs with behavioral problems. These medications should be used cautiously in dogs with conduction abnormalities, and clinicians should periodically monitor ECG and use good clinical judgment to weigh risks and benefits of medications for the safety of each dog. (*J Am Vet Med Assoc* 2000;216: 1571–1575)

Abnormal or problem behaviors are the number 1 reason that companion animals are euthanatized.[1-5] Approximately half to three-fourths of animals taken to shelters are euthanatized because of undesirable or problematic behaviors.[1] The most common behavioral problems in companion animals are rooted in anxiety[6] and commonly manifest as aggression, fear, and inappropriate elimination.[2,6] These animals often are treated with pharmacologic agents as part of an integrated treatment program involving behavioral modification.[7] Antianxiety medications directly treat the underlying anxiety and facilitate behavior modification.[6,8,9] Among the most used medications in veterinary behavioral medicine[6,8] are **tricyclic antidepressants (TCA)** such as amitriptyline,[a] nortriptyline,[b] imipramine,[c] doxepin,[d] and clomipramine.[e] Tricyclic antidepressants are well absorbed from the gastrointestinal tract and have extensive first-pass metabolism by the liver.[10] They are 70 to 95% protein bound and are highly lipid soluble.[8,10] Some TCA (eg, amitriptyline and imipramine) have active intermediate metabolites that are parent compounds (eg, nortriptyline and desipramine).[8,10,11] The TCA act primarily through blocking the reuptake of serotonin and norepinephrine.[6,8,9] Use of TCA has been associated with adverse effects, including cardiac abnormalities in humans.[10-15]

In humans, the most common potentially serious adverse cardiovascular effect associated with use of therapeutic TCA doses is orthostatic hypotension.[13,14] Mechanisms for this effect are not understood, although blockade of peripheral α-adrenergic receptors, stimulation of central α-adrenergic receptors, and a direct nonadrenergic effect have been implicated.[13]

Electrocardiographic effects observed in humans treated with TCA include sinus tachycardia and other arrhythmias; prolonged PR, QRS, QT, and **QT corrected for heart rate (QTc)** intervals; ST-T segment changes; bundle-branch block; and antiarrhythmic effects.[10,11,13] These changes rarely have clinical importance when standard therapeutic TCA doses are used,[11,13] but geriatric patients and those with cardiovascular disease, including conduction anomalies, constitute a population at greater risk for adverse cardiovascular effects.[15-17] Prolonged QT or QTc interval correlates exponentially with increased risk of malignant arrhythmia in some syndromes in humans,[18] but such data are not available for drug-induced prolongation.[19] It is not known whether these effects of TCA on the ECG are also evident or are problematic for dogs.

The purpose of the study reported here was to determine the effect of TCA administration on the ECG of dogs with behavioral conditions. Furthermore, correlations between ECG findings and serum concentrations of these medications were examined.

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Materials and Methods

Group 1 comprised 20 client-owned dogs that were not receiving other medications at the time of the study. Their weight ranged from 4.5 to 67.5 kg (9.9 to 148.5 lb; mean ± SD, 29.52 ± 17.02 kg [64.94 ± 37.44 lb]) and were between 9 and 103 months old (mean, 45.7 ± 29.89 months). Dogs in group 1 underwent complete physical and behavioral examinations. In addition, serum biochemical analyses, a CBC, and a 10-lead ECG were performed prior to initiating TCA treatment. Behavioral diagnoses included, but were not limited to, separation anxiety, dominance aggression, fear aggression, interdog aggression, food-related aggression, and thunderstorm and noise phobia. Amitriptyline was administered (range, 0.74 to 2.5 mg/kg [0.34 to 1.14 mg/lb] of body weight; mean, 1.39 ± 0.43 mg/kg [0.63 ± 0.20 mg/lb], PO, q 12 h for a duration of 49 to 150 days [mean, 100 ± 34.1 days]) to 17 dogs, and clomipramine was administered (range, 1.5 to 2.49 mg/kg [0.68 to 1.13 mg/lb]; mean, 2.06 ± 0.43 mg/kg [0.94 ± 0.20 mg/lb], PO, q 12 h for a duration of 56, 84, and 1,260 days to 3 dogs, with a minimum of 35 days at the highest dosage after it had been adjusted). After dogs had been receiving medication for ≥ 45 days, another 10-lead ECG was performed.

Group 2 comprised 19 client-owned dogs that had been receiving medication at the time of the study. Behavioral diagnoses for dogs in group 2 were similar to those for dogs in group 1. Eleven dogs were being treated with amitriptyline (range, 0.72 to 3.29 mg/kg [0.33 to 1.50 mg/lb]; mean, 1.6 ± 0.66 mg/kg [0.73 ± 0.30 mg/lb], PO, q 12 h for a duration of 80 to 1,170 days [mean, 338.7 days]). These 11 dogs ranged from 7.4 to 38.6 kg (16.3 to 84.9 lb) of body weight (mean, 24.19 ± 10.38 kg [53.22 ± 22.84 lb]) and were between 19 and 97 months old (mean, 50.91 ± 24.85 months). Eight dogs were being treated with clomipramine (range, 2.06 to 3.05 mg/kg [0.94 to 1.39 mg/lb]; mean, 2.55 ± 0.32 mg/kg [1.16 ± 0.14 mg/lb], PO, q 12 h for a duration of 60 to 270 days [mean, 322.5 ± 247.7 days]). These 8 dogs ranged from 9 to 41.1 kg (19.8 to 90.4 lb) of body weight (mean, 29.56 ± 11.03 kg [65.03 ± 24.27 lb]) and were between 16.5 and 106 months old (mean, 46.2 ± 35.4 months). Dogs in group 2 were evaluated with a single 10-lead ECG, and a serum sample was obtained to measure concentrations of TCA.

All ECG tracings were obtained while dogs were in a standing position. This position was selected instead of lateral recumbency to minimize handling of aggressive dogs. The following measurements were obtained for each ECG in lead II: heart rate, PR interval, P-wave duration and amplitude, **PR interval corrected for heart rate (PRc)**, QRS and QT intervals, QTc,[20] QTc/QT, and R-wave amplitude.[21,22] **Mean electrical axis (MEA)** of the ventricular depolarization process was calculated. To correct PR and QT for heart rate, PRc or QTc were calculated as PR or QT interval, respectively, divided by the square root of the duration of the cardiac cycle (in millimeters); duration of the cardiac cycle was the mean for 15 consecutive cycles.

Fresh blood samples were collected without serum separators. Shortly after clotting, samples were centrifuged, and serum was decanted into a clean tube. We chose serum rather than plasma, because results are the same for serum and plasma in humans.[23] Plasma is often used to determine TCA concentrations in humans to avoid the possibility of error such as inappropriate use of serum separators while processing samples, because serum separators used in processing serum samples can falsely lower the apparent TCA concentration. The samples were frozen for ≤ 6 months. Subsequently, they were analyzed, using a fluorescence polarization immunoassay. Concentrations reported are total amount of TCA and their demethylated intermediates, which are metabolically active. The fluorescence polarization immunoassay cannot distinguish between parent compounds and their demethylated metabolites.

We did not attempt to obtain blood pressure measurements in an attempt to minimize handling of potentially aggressive dogs. Furthermore, the authors believe that orthostatic hypotension in dogs is a poorly defined clinical entity that is difficult to measure reliably.

To compare values for the ECG of dogs in group 1 before receiving medication with those for the same dogs after receiving medication for ≥ 45 days, we computed the difference value (ie, after value – before value) for every variable and tested the null hypothesis that the mean of the observed difference values did not differ significantly from 0. Parametric *t*-tests were used when data were normally distributed, and Wilcoxon matched pairs signed rank tests were used when data were not normally distributed. The ECG values for dogs in group 2 were compared the same way as for those in group 1, using the mean of the values for dogs in group 1 before receiving medication and the reference range for our veterinary medical teaching hospital. Tests of correlation among variables were performed, using Pearson product-moment correlation tests when data were normally distributed and nonparametric procedures (the Spearman rank correlation test) for data that were not normally distributed. Significant differences were defined as $P < 0.05$.

Results

Rhythm disturbances or electrical axis deviation were not evident in any of the dogs, except for 1 dog receiving clomipramine that had evidence of a right bundle-branch block. All dogs had normal sinus rhythm or sinus arrhythmia. In dogs of group 1, the ECG measurements and calculated values obtained after receiving medication did not differ significantly from those for the ECG measurements and calculated values obtained before receiving medication.

The ECG measurements and calculated values obtained for dogs of group 2 did not differ significantly, compared with the mean of the dogs of group 1 before receiving medication or the reference range for dogs without cardiac disease examined by the cardiology service at our veterinary medical teaching hospital. Reference range values were as follows: P-wave amplitude, ≤ 0.4 mV; P-wave duration, ≤ 60 milliseconds; PR interval, ≤ 150 milliseconds; QRS interval, ≤ 70 milliseconds; QT interval, 200 ± 40 milliseconds; R-wave amplitude, ≤ 3.0 mV; and 0 degrees < MEA < 90 degrees.

Serum concentrations for dogs in group 2 receiving amitriptyline ranged from < 20 to 351.3 ng/ml (mean, 112.9 ± 113.6 ng/ml). Serum concentrations for dogs in group 2 receiving clomipramine ranged from < 20 to 761.7 ng/ml (mean, 401.8 ± 226.2 ng/ml).

Regression analysis comparing serum concentrations of TCA and each of the ECG measurements was performed. The P-wave duration had a significant positive correlation ($r = 0.767$; $P = 0.026$) with serum concentrations of clomipramine (**Fig 1**), whereas P-wave duration had a significant negative correlation ($r = –0.633$; $P = 0.037$) with serum concentrations of amitriptyline (**Fig 2**). The QTc interval had a significant negative correlation ($r = –0.626$; $P = 0.039$) with serum concentrations of amitriptyline (**Fig 3**), whereas serum concentrations of clomipramine were not significantly correlated with QTc (**Fig 4**).

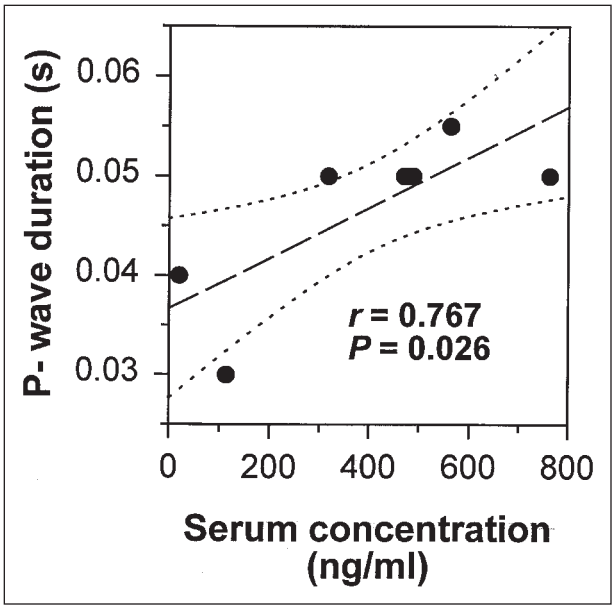

Figure 1—Regression analysis of the association between serum concentrations of clomipramine and P-wave duration in 8 dogs (2 data points overlap). Dashed line indicates regression lines. Dotted lines indicate the 95% confidence intervals.

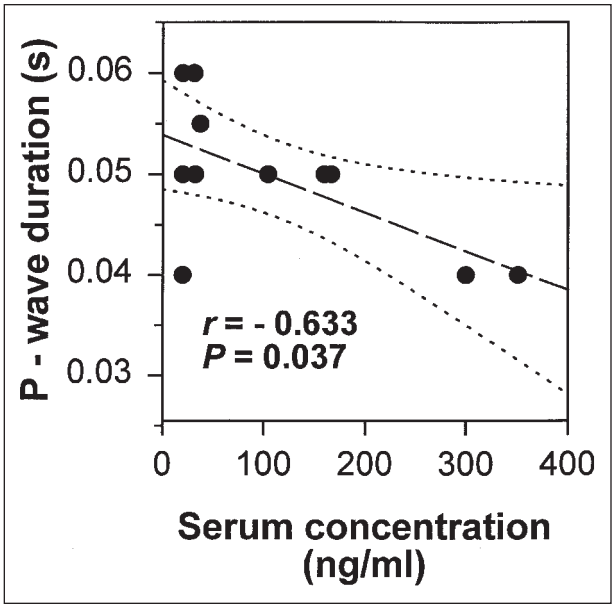

Figure 2—Regression analysis of the association between serum concentrations of amitriptyline and P-wave duration in 11 dogs. *See* Figure 1 for key.

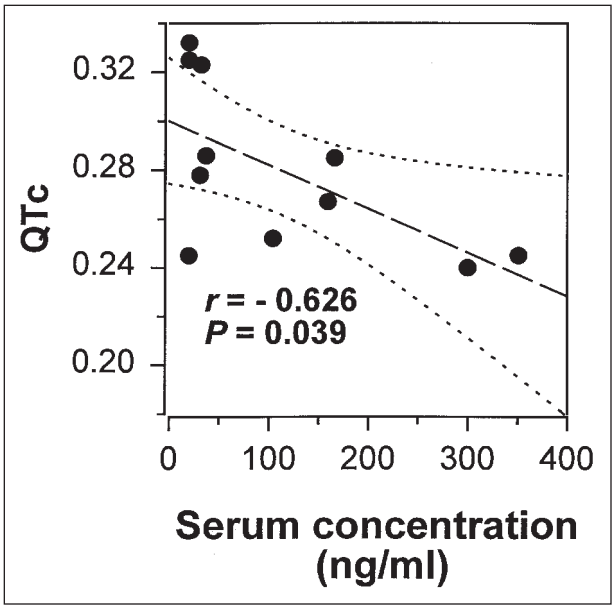

Figure 3—Regression analysis of the association between serum concentrations of amitriptyline and QT interval corrected for heart rate (QTc) in 11 dogs. *See* Figure 1 for key.

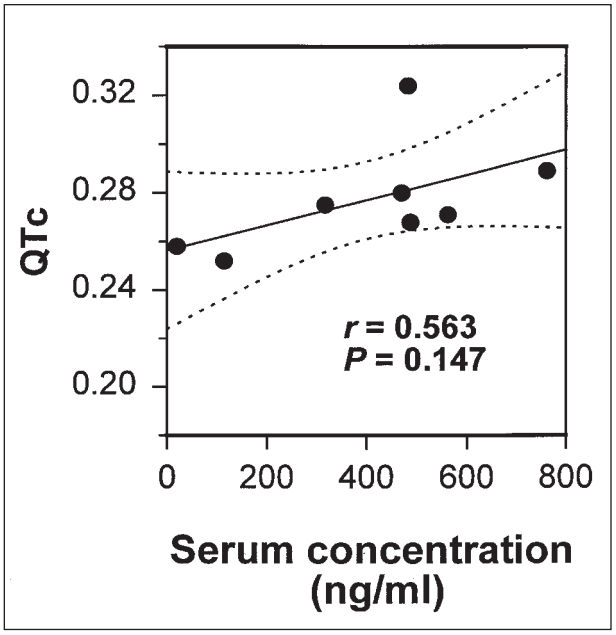

Figure 4—Regression analysis of the association between serum concentrations of clomipramine and QTc interval in 8 dogs. *See* Figure 1 for key.

Discussion

In human patients, determining plasma or serum TCA concentration is clinically useful as a means of avoiding toxic effects and of maximizing response to medication.[23] In humans, cardiac effects have been detected for TCA concentrations as low as 50 to 100 ng/ml. With concentrations > 500 ng/ml, the incidence of serious cardiac toxicity increases significantly.[24] Ranges for plasma concentration of TCA considered optimal in humans are 150 to 300 ng/ml (amitriptyline, imipramine), 50 to 150 ng/ml (nortriptyline), and 125 to 300 ng/ml (desipramine), although there is little relationship between plasma concentration and antidepressant response with most antianxiety medications.[23] In humans, TCA reach peak plasma concentrations in 8 to 12 hours and steady-state concentrations after 5 to 7 days; however, a 30- to 50-fold difference in plasma concentrations of individuals given the same dose has been reported.[8,12] In dogs, the plasma half-life of clomipramine has been established at therapeutic dosages, and it ranges from approximately 2 to 9 hours in fed dogs to 3 to 21 hours when given to dogs from which food has been withheld.[9] This difference may be attributed to pro-

longed drug absorption in dogs from which food has been withheld.[9]

In the dogs of the study reported here, the use of TCA did not appear to be associated with ECG abnormalities, because all but 1 of the ECG tracings in this study were interpreted as nonremarkable. The single ECG considered abnormal was from a dog in group 1 that did not have clinical signs of cardiovascular disease; this dog had been receiving clomipramine for 1,260 days and had a serum concentration of 183.2 ng/ml (we had incomplete data for serum concentrations of dogs in group l, so an analysis was not performed). The ECG recorded from that dog revealed a right bundle-branch block. Right bundle-branch block is infrequently found in healthy dogs and usually is considered to be a benign incidental clinical finding.[25,26] A complete cardiac evaluation, including echocardiography and radiography, was recommended to rule out cardiac disease, but the client elected not to have the evaluation performed. It was also recommended that the client discontinue giving the dog clomipramine to determine whether there would be a change in the right bundle-branch block, but the client elected to continue giving clomipramine because of the vast improvement of the dog's behavioral condition with that treatment. Thirteen months after diagnosis of the right bundle-branch block, results of cardiac auscultation were considered normal.

The differential and opposing correlations of serum concentrations of the 2 TCA on ECG indices is an important finding. There was a positive correlation of increasing serum concentrations of clomipramine on P-wave duration, but amitriptyline had a negative correlation. The QTc interval was not correlated with serum concentrations of clomipramine, but there was a negative correlation on QTc interval seen with increasing serum concentrations of amitriptyline. This finding seems especially intriguing in light of the reported prolongation of QTc in humans treated with TCA.[11,13] In this regard, if indeed a prolonged QTc interval correlates with an increased risk of malignant ventricular arrhythmia,[18] amitriptyline treatment in dogs may actually decrease this theoretic risk. These effects may be important when a dog treated with TCA develops conduction abnormalities. Analysis of our results indicates that clinically relevant doses of some TCA appear to be electrophysiologically safe, at least as determined by evaluation of the ECG. This finding is in agreement with a study[f] in which high doses of clomipramine (12 or 20 mg/kg [5.45 or 9.09 mg/lb]) in 8 dogs produced sinus bradycardia with sinoatrial block, second-degree atrioventricular block, and physiologic ventricular escape beats in ≤ 4% of the recordings.

The use of pharmacologic intervention is often an important part of treating behavior problems, and the importance of a thorough physical examination, including cardiac auscultation and laboratory evaluation (eg, serum biochemical analyses and a CBC), prior to administration of these medications cannot be overemphasized. Laboratory evaluation is necessary to rule out metabolic disorders contributing to behavior problems as well as to assess apparent organ function for the metabolism and elimination of the medications. For safety of an animal, an ECG evaluation is recommended prior to and throughout the course of treatment with TCA whenever rhythm disturbances are suspected during cardiac auscultation or during arterial pulse palpation. Special attention should be given to measurable electrocardiographic intervals, particularly when there is evidence for aberrant intracardiac conduction or when the animal is of an age or breed considered at risk for developing cardiac disease. It is advisable to compare electrocardiographic intervals between baseline (pretreatment) ECG and those obtained during follow-up visits conducted after long-term treatment with TCA has been instituted.

Two other populations of animals need to be evaluated in a similar manner. One population is cats and other animals treated with psychopharmacologics such as selective serotonin-reuptake inhibitors or benzodiazepines. The second population includes those animals receiving a combination of pharmacotherapeutic agents.

[a]Elavil, Zeneca Pharmaceuticals, Wilmington, Del.
[b]Pamelor, Novartis Pharmaceuticals, East Hanover, NJ.
[c]Tofranil, Novartis Pharmaceuticals, East Hanover, NJ.
[d]Sinequan, Pfizer Labs, New York, NY.
[e]Clomicalm, Novartis Animal Health, Greensboro, NC.
[f]Pouchelon JL, Martel E, Champeroux P, et al. Effect of clomipramine on the electrocardiogram, heart rate and intra-ocular pressure of dogs (abstr), in *Proceedings*. 17th Am Coll Vet Intern Med Forum 1999;714.

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