Effects of clomipramine hydrochloride on heart rate and rhythm in healthy dogs

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Objective—To determine the effects of clomipramine hydrochloride on heart rate and rhythm in dogs.

Animals—17 healthy Beagles.

Procedures—In experiment 1, 8 dogs received placebo or clomipramine (20 mg/kg of body weight, q 24 h, PO) for 7 days in a 2-way crossover design. In experiment 2, 9 dogs were evaluated for 48 hours before and 24 hours after oral administration of clomipramine (4 or 12 mg/kg) in a 2-way crossover design. Electrocardiogram and heart rate were monitored continuously by use of telemetry.

Results—A significant diurnal rhythm in heart rate was detected; minimum values were recorded at night. Administration of 20 mg of clomipramine/kg induced a significant reduction in heart rate, with peak effect achieved approximately 12 hours after dosing. Administration of 4 or 12 mg of clomipramine/kg did not result in significant changes in heart rate. Sinoatrial and second-degree atrioventricular block and ventricular escape beats were observed during periods of slow heart rate in more dogs that received clomipramine (3 to 4 of 8 dogs), compared with dogs that received placebo (1 to 2 of 8 dogs), but this difference was not significant.

Conclusions and Clinical Relevance—Short-term administration of clomipramine induced benign cardiovascular effects in dogs rather than the potentially dangerous arrhythmias or tachycardia reported following administration of tricyclic antidepressants to humans. Precautions regarding cardiovascular effects may not be needed for the use of clomipramine in healthy dogs. (*Am J Vet Res* 2000;61:960–964)

In human medicine, clomipramine hydrochloride is classified as a **tricyclic antidepressant (TCA)** with serotonin reuptake inhibiting properties. It is effective in the treatment of several central nervous system disorders, including anxiety, depression, and stereotypies.[1,2] In humans, 2 mechanisms of action appear relevant[2]: inhibition of neuronal reuptake of serotonin and noradrenaline, which is responsible for the drug's efficacy, and antagonism of cholinergic muscarinic receptors, which accounts for most of the adverse effects of the drug. In humans, most of the adverse effects (eg, dry mouth, hot skin) are not considered serious, although they may be an important obstacle to compliance with treatment.[1,2] Other adverse effects, although rare, are potentially serious. Clomipramine, in common with other TCA, can increase heart rate, decrease blood pressure, and slow intracardiac conduction.[3-5] The quinidine-like class 1A antiarrhythmic effect is manifested as changes to the ECG, such as prolonged PR intervals, increased QRS duration, and increased rate-corrected QT intervals.[3,5,6] These effects are only rarely associated with clinical consequences,[3,4,7] but in the United States, the label for clomipramine carries a warning to use the drug with caution in humans with cardiovascular disease. Moreover, clomipramine is contraindicated during the acute recovery period after a myocardial infarction.

Clomipramine is now registered in many countries, including the United States, for use in dogs, and it is effective in reducing stereotypic and anxiety behaviors in dogs.[8-12] Some authors have recommended using clomipramine with caution in dogs with preexisting cardiovascular disease.[13,14] However, there are differences in the metabolism of the drug between dogs and humans that may result in a reduced potential for development of adverse effects in dogs, especially those of anticholinergic or noradrenergic origin.[15-17] In dogs, the anticholinergic properties of clomipramine are manifested only at toxic doses (14 mg/kg of body weight, IV).[18] The cardiovascular effects of IV administered clomipramine have been studied in anesthetized dogs,[18-23] but the results are probably not directly relevant to clinical practice in which clomipramine is administered orally to conscious animals.

To our knowledge, the effects of clomipramine, administered at therapeutic dosages (up to 4 mg/kg, q 24 h, PO), on the cardiovascular system have not been studied in dogs. The purpose of the study reported here was to determine the effects of clomipramine, administered at five times the therapeutic dose or at lower doses, on heart rate and rhythm in healthy dogs.

Materials and Methods

Animals—17 healthy Beagles were housed in a climate-controlled animal house. An artificial day-night cycle was maintained, with 12 hours of light starting at 7:30 AM followed by 12 hours of darkness. The dogs were fed 400 g of a commercial diet[a] once daily. Water was provided ad libitum. Body weight and clinical condition were monitored at least once daily throughout the study.

Placement of ECG electrodes—At least 5 days prior to the study, dogs were anesthetized with thiopentone[b] (20 mg/kg, IV) and halothane[c] (1 to 5%, administered via a rebreathing circuit) to allow placement of ECG electrodes in

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the lead-II position. The electrodes were connected to a telemetric transmitter[d] placed into the pocket of a jacket worn around the thorax. Postoperative pain was controlled as needed with buprenorphine (5 µg/kg, IM).[e]

Experimental protocol—In experiment 1, 8 dogs (4 males and 4 females) between 7 and 23 months old and weighing between 11.6 and 15.4 kg were used. Placebo or clomipramine (20 mg/kg) were administered orally for 7 consecutive days, according to a 2-part crossover design with a minimum washout period of 1 week between treatments. Test tablets contained 5, 20, or 80 mg of clomipramine (as the hydrochloride) and a meat flavor.[f] Placebo consisted of microcrystalline cellulose[g] in gelatin capsules. Clomipramine and placebo were administered with a small amount of food between 8 and 11 AM. Plasma biochemical analyses and CBC were performed before administration of the first and last dose of clomipramine or placebo.

Electrocardiograms and heart rate were recorded by use of telemetry.[24] Electrocardiograms were recorded for 30 seconds every 15 minutes throughout each 7-day treatment period, using a sampling rate of 500 Hz. Data were collected and analyzed, using biotelemetry receivers and a computerized acquisition system.[h] Electrocardiograms were checked and arrhythmias classified by an experienced veterinary cardiologist (JLP). The heart rate was determined automatically from the R-R interval of the ECG recorded for 30 seconds immediately before and at the following times after administration of placebo or clomipramine: 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours after treatment on days 1 and 7, and 4, 8, 12, and 24 hours after treatment on days 2 through 6. For recording, dogs were placed into individual stainless steel cages and allowed to move freely.

In experiment 2, a single dose of clomipramine (4 or 12 mg/kg, PO) was administered to 9 Beagles between 7 and 15 months old and weighing between 11.6 and 14.4 kg according to a 2-part crossover design with a washout period of at least 7 days between treatments. For technical reasons, 1 male dog given 4 mg of clomipramine/kg in the first arm of the crossover was replaced by another male dog in the second arm, to give a total of n = 8 in both arms of the crossover. The 48-hour pretreatment period was considered the control period. Clomipramine was administered with a small amount of food between 8 and 9 AM. Plasma biochemical analyses and CBC were performed immediately before and 24 hours after treatment.

The same apparatus used in experiment 1 was used to record ECG and heart rate in experiment 2. Electrocardiograms were recorded for 30 seconds every 15 minutes throughout the 48-hour pretreatment period and for 24 hours after treatment. Heart rate was recorded for 30 seconds immediately before and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours after treatment.

Statistical analyses—Heart rates after administration of clomipramine were compared with those after administration of placebo (experiment 1) or during the 48-hour pretreatment control period (experiment 2). In a first analysis, heart rate was assumed to depend on time and treatment, where treatment effects were time specific. Individual measurements were assumed to depend on each other, according to an autoregressive covariance structure (ie, consecutive measurements were highly correlated, and more distant ones were less so). Dogs were modeled as a random effect (ie, baseline heart rates varied within the population). Parameters were estimated, using ANOVA for repeated measures,[i] with absolute time and treatment-time interaction as fixed factors, animal as a random effect, and an autoregressive variance structure for one time series of measurements. In the event of a significant F statistic, posthoc comparisons were made at each time, using a Student *t*-test with no correction for multiple analyses. A second model for ANOVA was also tested, in which the heart rate was assumed to depend only on the time of day during repeated treatment on days 2 to 7.

Frequency with which arrhythmias were detected during each recording was defined as the number of records with arrhythmias in relation to the total number of records. In the event that different arrhythmias were detected in the same dog during the same recording period, each type of arrhythmia was recorded as a separate incident. Frequency of all arrhythmias was compared between groups by use of the Fisher exact test.[j]

Effects of clomipramine on body weight and results of CBC and plasma biochemical analyses were analyzed by use of ANOVA for repeated measures.

In all cases, a two-tailed α-level of 0.05 was used.

Results

Experiment 1—Body weight and results of CBC and plasma biochemical analyses did not differ during the experiment in dogs that received placebo or clomipramine. During the 7-day treatment period, 1 dog that received clomipramine vomited between 2 and 3 hours after dosing on days 2 and 6, and 1 dog vomited between 2 and 3 hours after dosing on days 2 and 3. Other abnormal clinical signs were not detected in any other dogs.

A diurnal pattern to heart rate was detected in dogs that received placebo, with the slowest rate recorded at night (**Fig 1 and 2**). Clomipramine induced a decrease in heart rate that was maximal 12 hours after dosing on the first day. Similar heart rate profiles as those recorded on day 1 were observed on days 2 to 7 in clomipramine and placebo groups. A significant effect of time and a significant time-treatment interaction were observed. Significance was also obtained for an alternative model, in which heart rate was assumed to depend only on the time of day during repeated treatment on days 2 through 7 (ie, heart rate varied periodically during each 24-hour period). Therefore, we concluded that heart rate changed over

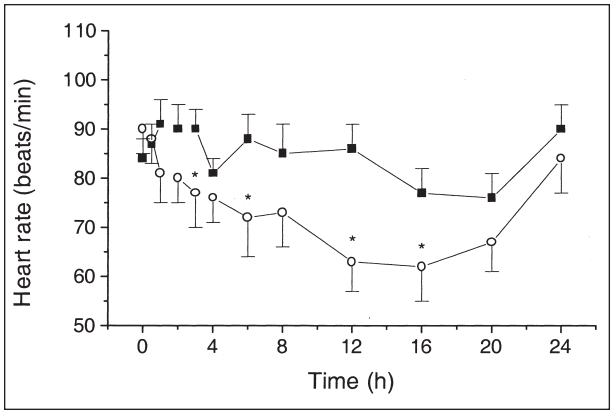

Figure 1—Mean (± SEM) heart rates determined by use of telemetry in 8 Beagles that received placebo (■) or clomipramine hydrochloride (20 mg/kg, PO, q 24 h; ○) between 8 and 11 AM for 7 days (0, 24, 48, 72, 96, 120, and 144 hours). Significant ($P < 0.001$; ANOVA for repeated measures) effects of time and time-treatment interaction were observed. *Values significantly ($P < 0.05$; *t*-test) different between groups.

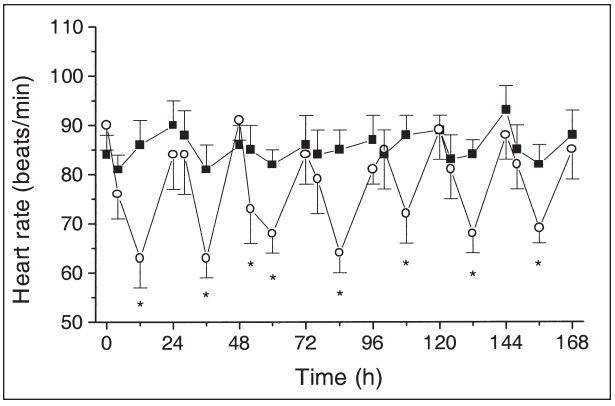

Figure 2—Mean (± SEM) heart rates determined by use of telemetry in 8 Beagles after administration of the first of 7 doses of placebo (■) or clomipramine (20 mg/kg, PO; ○) at 0 hours. Significant ($P < 0.001$; ANOVA for repeated measures) effects of time and time-treatment interaction were observed. *Values significantly ($P < 0.05$; *t*-test) different between groups.

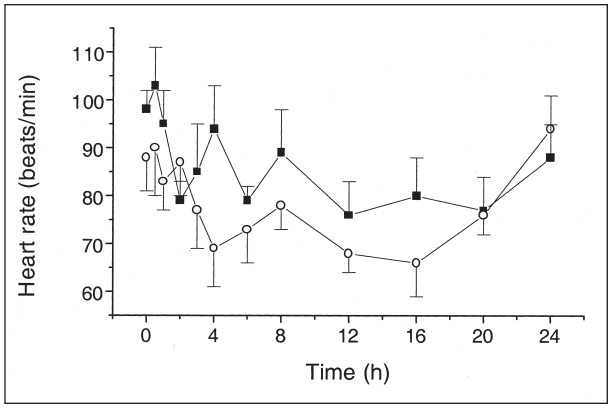

Figure 3—Mean (± SEM) heart rates determined by use of telemetry in 8 Beagles during the final 24 hours of a 48-hour pretreatment control period (■) and after administration of a single dose of clomipramine (4 mg/kg, PO; ○) at 0 hours. A significant ($P < 0.001$) effect of time but not of treatment ($P = 0.14$) was detected by use of ANOVA for repeated measures.

time, and clomipramine had a significant influence on this change. Posthoc comparisons revealed a significant effect of clomipramine (reduction in heart rate) at the following times: 3, 6, 12, 16, 36, 52, 60, 84, 108, 132, and 156 hours after initiation of the experiment. In other words, a significant effect of clomipramine was observed on all days 12 hours after dosing and on certain days 3, 4, 6, and 16 hours after dosing. Significant effects of clomipramine on heart rate were not detected 24 hours after dosing on any day.

Disturbances in the ECG were detected for only 1 dog that received placebo. This dog developed **second-degree atrioventricular block (AVB2)** that was apparent during transient periods of bradycardia 10 and 17 hours after administration of the seventh and final dose of placebo. This occurred in 2 (0.3%) of the 672 traces.

Minor ECG disturbances were observed in 3 of the 8 dogs that received clomipramine. Changes consistent with AVB2 were detected in 1 dog on day 7 approximately 20 hours after dosing. Ventricular escape beats

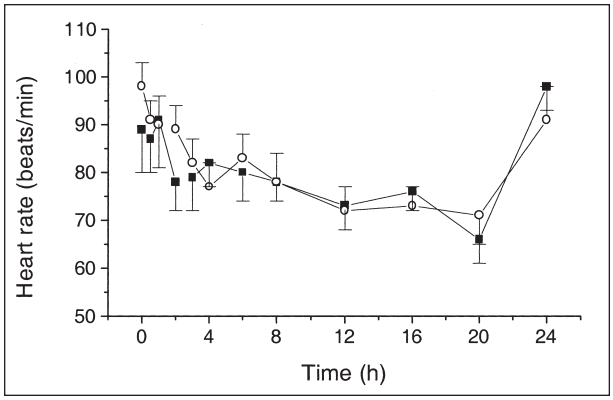

Figure 4—Mean (± SEM) heart rates determined by use of telemetry in 8 Beagles during the final 24 hours of a 48-hour pretreatment control period (■) and after administration of a single dose of clomipramine (12 mg/kg, PO; ○) at 0 hours. A significant effect of time ($P < 0.001$) but not of treatment ($P = 0.66$) was detected by use of ANOVA for repeated measures.

were detected in a second dog on days 1, 2, 3, and 7 between 10 and 22 hours after dosing and in a third dog on days 7 and 8 approximately 20 hours after dosing. All changes in the ECG were detected when heart rate was slow. Electrocardiogram disturbances were detected in 2 to 15 (0.3 to 2.2%) of the 672 traces obtained for each dog throughout the 7-day recording period. Frequency of ECG disturbances were not significantly different between dogs that received placebo and those that received clomipramine. Changes in the PQ or PR interval or in the amplitude or length of the QRS complex were not detected in any dog.

Experiment 2—Results of CBC and plasma biochemical analyses after treatment did not differ from values obtained before treatment. Clinical status also did not change.

A significant effect of time on heart rate was detected during the pretreatment control period and after treatment, with minimum heart rates recorded during the night **(Fig 3 and 4)**. However, we did not detect significant effects of clomipramine at either dose (4 mg/kg and 12 mg/kg) used. In a post-hoc comparison, heart rate recorded 4 hours after administration of 12 mg of clomipramine/kg was significantly less than rate recorded at 4 hours during the pretreatment period; however, mean heart rate during the control period was high at 4 hours.

Therefore, we concluded that administration of 4 or 12 mg of clomipramine/kg did not have a significant effect on heart rate.

Minor disturbances of the ECG, manifested as **sinoatrial block (SAB)** in 2 dogs and ventricular escape beats in 2 dogs, were observed in 4 of the 8 dogs after administration of 4 mg of clomipramine/kg. These events were detected in 1 (1%) of the 96 traces obtained for each dog throughout the 24-hour recording period. Second-degree atrioventricular block was observed in 2 of 8 dogs before treatment (1/192 [0.5%] traces for each dog).

Second-degree atrioventricular block was observed in 3 of 8 dogs after administration of 12 mg of clomipramine/kg (1 to 4 of 96 [1 to 4.2%] traces for each

dog). In 1 dog, SAB was observed in 1 of 192 (0.5%) traces before treatment and in 3 of 96 (3%) traces after administration of 12 mg of clomipramine/kg. All disturbances were detected during periods of slow heart rate and occurred mainly at night. Frequency of ECG disturbances after treatment was not significantly different, compared with frequency before treatment.

Discussion

In this study, we found that clomipramine at a dose of 20 mg/kg administered orally induced a significant slowing of the heart rate in healthy, conscious Beagles. Clomipramine induced a nonsignificant reduction in heart rate at a dose of 12 mg/kg and had no effect at a dose of 4 mg/kg. Electrocardiographic changes (ie, SAB, AVB2, and ventricular escape beats) were recorded during periods of bradycardia. Although these arrhythmias were detected in more dogs treated with clomipramine than in placebo-treated or control dogs, differences between groups were not significant. We considered the observed arrhythmias to be benign, because SAB, AVB2, and ventricular escape beasts are normal physiologic events that occur during periods of slow heart rate in dogs.[25] All of the arrhythmias were detected sporadically; maximum frequency of arrhythmias in any dog treated with clomipramine was 4% of all traces. This result emphasizes the value of long-term monitoring of ECG, which we achieved by use of telemetry.[24] Telemetry has the additional advantage of recording ECG in conscious, unrestrained animals.

We did not observe any of the cardiovascular effects of TCA previously described in humans. At therapeutic doses in humans, TCA can increase heart rate, reduce blood pressure, and slow intracardiac conduction, which leads to such changes to the ECG as prolonged PR intervals, increased QRS duration, and increased rate-corrected QT intervals.[3-5,7] The effects we observed in dogs are similar to the effects of **selective serotonin reuptake inhibitors (SSRI)**, which reduce heart rate in dogs and humans.[5,26,27] In humans, the most widely studied SSRI, fluoxetine, induces slight bradycardia in healthy volunteers and depressed patients, but only rarely induces adverse cardiovascular events such as serious arrhythmias.[5,26,28] Infusion of fluoxetine at doses slightly greater than the therapeutic dose in anesthetized dogs led to slight and nonsignificant bradycardia and reduction in stroke volume but no evidence of changes in intracardiac conduction.[27] In that same study, amitriptyline induced cardiac effects typical of a TCA (eg, tachycardia, reduced blood pressure, negative inotropic effects, and arrhythmias).

In anesthetized dogs, intravenously administered clomipramine induced stimulatory effects (tachycardia and increased myocardial contractility) at a low dose (0.0625 mg/kg), whereas higher doses (≥ 1 mg/kg) induced inhibitory effects such as bradycardia and decreased blood pressure and myocardial contractility.[19] Equivalent results have been described in other studies.[18,20-23] However, results of these studies may not be directly relevant to the clinical use of clomipramine, because the drug was administered intravenously. Intravenous administration leads to initially higher plasma concentrations of clomipramine, compared with oral administration.[16] Moreover, the general anesthetic itself may have an influence on cardiovascular variables. Results of the present study indicated that clomipramine administered at a therapeutic dose (4 mg/kg, PO) to healthy, conscious dogs did not affect heart rate or ECG. At a moderately high dose (20 mg/kg, PO), heart rate decreased. Results of all of these studies suggest that several different cardiovascular responses may develop in dogs after administration of clomipramine. These various responses could develop via different mechanisms, because clomipramine can affect several transmitter systems.[17,29] We speculated that bradycardia detected in our dogs after administration of 20 mg of clomipramine/kg was a result of serotoninergic effects, similar to responses detected in dogs and humans after administration of a SSRI. An increase in brain serotonin concentration reduces central sympathetic outflow, and, therefore, SSRI may reduce sympathetic tone.[26,27,30] Tachycardia and increased myocardial contractility could be caused by anticholinergic properties of clomipramine or inhibition of the neuronal reuptake of noradrenaline, equivalent to the effects detected in humans after administration of a TCA and in dogs after administration of amitriptyline.[19,27] Finally, the inhibitory cardiovascular effects of clomipramine after administration of high doses may be the result of a direct myocardial-depressant action.[19] These mechanisms are consistent with results of pharmacokinetic trials in dogs,[15-17] which suggest that clomipramine, administered at therapeutic doses, should preferentially inhibit neuronal reuptake of serotonin.[17]

In humans, TCA can induce tachycardia and arrhythmias.[6,26] However, with the exception of overdose and administration after myocardial infarction, the cardiovascular effects of TCA in humans may have little clinical relevance.[3,7] Even in patients with myocardial infarction, the benefits of the antidepressant effects of TCA may outweigh the risk of adverse effects.[31] It has been assumed that clomipramine has the same cardiovascular effects in dogs as in humans and, therefore, clomipramine should be used with caution.[13,14] Results of the present study suggest that clomipramine should present minimal or no cardiovascular risk to dogs without cardiovascular disease. Even in dogs with congestive heart failure, clomipramine may be beneficial, because slowing of the heart rate is a target for treatment of congestive heart failure, and anxiety may play a role in the morbidity of heart failure. It is important to emphasize that we studied the effects of clomipramine only during short-term administration (7 days); we cannot make definitive conclusions about the cardiovascular effects of this drug during long-term treatment. In addition, the use of clomipramine in dogs with bradycardia or severe heart failure merits special caution. Reliable recommendations can only be made after the effects of clomipramine are evaluated in high-risk dogs.

Two observations can be made regarding the time course of the heart rate response to clomipramine (Fig 1). First, there was no change in the response during repeated administration of 20 mg of clomipramine/kg for 7 days, suggesting that the mechanism that resulted in a decreased heart rate was fully activated after the

first dose. However, results of kinetic studies indicate that once-a-day oral administration of 20 mg of clomipramine/kg should lead to substantial bioaccumulation of clomipramine and desmethylclomipramine during the first few days of treatment, with steady state conditions being achieved in ≥ 4 days.[17] Second, the effect of clomipramine on heart rate reached a maximum approximately 12 hours after dosing. This time course does not correlate with plasma clomipramine or desmethylclomipramine concentration profiles; both reach peak concentrations approximately 1 hour after oral dosing and are rapidly eliminated ($t_{1/2} \leq 4$ hours).[16,17] From these observations, we concluded that the cardiovascular effects do not correlate directly with plasma concentrations of clomipramine or desmethylclomipramine. Rather, our results are consistent with an indirect or centrally mediated mechanism of action. Most of the anti-anxiety and antistereotypic actions of clomipramine are assumed to be caused by inhibition of neuronal reuptake of serotonin,[8,9,11] and we hypothesize that the heart rate lowering effects are achieved via a similar mechanism. Therefore, assuming once-a-day administration, we speculate that clomipramine may be most effective when administered approximately 12 hours before the desired maximal effect (eg, 12 hours before the owners leave the house in a case of separation anxiety). However, this speculation requires further testing.

[a]125 Cl, Usine d'alimentation rationelle, Epinay sur Orge, France.
[b]Nesdonal, Rhone Merieux, Lyon, France.
[c]Halothane, Laboratoires Belamont, Neuilly sur Seine, France.
[d]TA 10CTA-D70-PC or Tl 10CTA-D70-PC, Data Sciences International, St Paul, Minn.
[e]Temgésic, Schering Plough, Levallois-Perret, France.
[f]Clomicalm, Novartis Animal Health Inc, Basel, Switzerland.
[g]Abicel PH102, Merck, Darmstadt, Germany.
[h]RLA2000 and LABPRO, Data Sciences International, St Paul, Minn.
[i]PROC MIXED release 6.11, SAS Institute, Cary, NC.
[j]RS/1 Software, Release 5.2.3, BBN Software, Cambridge, Mass.

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