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Results of a follow-up investigation to a clinical trial testing the efficacy of clomipramine in the treatment of separation anxiety in dogs

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Abstract

The objective of the study was to investigate the incidence of adverse events and changes in behaviour after use of clomipramine to treat separation anxiety in dogs. This study was a follow-up investigation to a previously published clinical trial. In the main trial, dogs were randomised in a double-blinded manner to receive placebo, standard (1–2 mg/kg, q12h) or low (0.5–1 mg/kg, q12h) dosages of clomipramine for 2–3 months. All dogs received behavioural therapy. Follow-up questionnaires were completed in 76 out of 89 dogs between 5.5 and 16 months after completion of the main trial.

Post study, 12 dogs at one site received clomipramine long term (>13–16 months). The clomipramine was tolerated well, no dogs had worsening of their behaviour and behaviour improved further in 10 (83%) dogs.

An additional 16 dogs received clomipramine and/or other drugs for up to 30 weeks and 48 cases received no drugs post trial. Acute worsening of behaviour was noted in the first two weeks after stopping treatment in three cases receiving low dose clomipramine, but in no cases in the other groups. The worsening rate of separation anxiety >2 weeks after stopping therapy was 13% of dogs that had received standard-dose clomipramine, 15% of dogs that had received low dose clomipramine and 23% of dogs that had received placebo. The mean time to worsening was longer in dogs that had received standard-dose clomipramine (37 weeks), as compared to low dose clomipramine (11 weeks, $P = 0.005$) or placebo (11 weeks, $P = 0.003$).

In conclusion, no undesirable long term effects were detected in the use of standard-dose (1–2 mg/kg, q12h) clomipramine for the treatment of separation anxiety in dogs. Abrupt withdrawal of a sub-optimal

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dose of clomipramine (0.5–1 mg/kg, q12h) before signs of anxiety have been well controlled is not recommended.

Keywords: Clomipramine; Separation anxiety; Dog

1. Introduction

We have described previously results of a clinical trial to test the efficacy of clomipramine as an aid in the treatment of separation anxiety in dogs (King et al., 2000). The study was a prospective, randomised and blinded trial. All dogs received behavioural therapy and were randomised to receive either placebo or two different dosages of clomipramine (standard: 1–2 mg/kg, q12h; low: 0.5–1 mg/kg, q12h) for 56–84 days. The results showed that, as compared to placebo, the standard dosage of clomipramine produced significant reductions in signs of anxiety (destruction, defecation, urination and vocalisation) during the trial. The major benefit of clomipramine was to produce a faster reduction in signs of anxiety, as compared to placebo. Beneficial effects of clomipramine in separation anxiety have been described in one other clinical trial (Petit et al., 1999), but not in another (Podberscek et al., 1999).

In this paper, we describe the results of a follow-up investigation after the completion of the main study. Information was collected on the management of the dogs, the appearance of any adverse events following cessation of therapy, and the incidence of return of signs of separation anxiety. Two possible problems could have been anticipated. First, abrupt withdrawal of clomipramine might have led to acute worsening of the dog's condition, analogous to the "acute withdrawal syndrome" described in humans when therapy with selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA) or monoamine oxidase inhibitor (MAOI) drugs are stopped suddenly (Lejoyeux et al., 1996; Hewson et al., 1998). Second, the original disorder of separation anxiety might have recurred after clomipramine treatment was stopped. "Relapse" of the original condition has been described in humans with panic attacks and stereotypies once clomipramine has been withdrawn (Modigh, 1990; McTavish and Benfield, 1990; Dodson, 1991). Return of signs of stereotypies has also been reported in dogs after cessation of treatment with clomipramine (Overall, 1994; Mertens and Dodman, 1996; Moon-Fanelli and Dodman, 1998).

The study consisted of a telephone interview with the dog's owner between 5 and 16 months after completion of the main clinical trial.

2. Animals, materials and methods

2.1. Original study

The original (termed "main") clinical trial has been described in detail previously (King et al., 2000). Dogs with separation anxiety received behavioural therapy and, in addition, were assigned randomly in a blinded manner one of the following treatments:

1. 1.0–2.0 mg/kg, PO, q12h, clomipramine ["standard-dose"], 26 dogs;
2. 0.5–1.0 mg/kg, PO, q12h, clomipramine ["low dose"], 33 dogs;
3. Placebo, PO, q12h, 30 dogs.

All dogs were treated for 56 or 84 days. Veterinary examinations plus behavioural and veterinary follow-ups were made on days 0, 28, 56 and, in some cases, on day 84. The primary measure of efficacy was the frequency of signs of anxiety (destruction, defecation, urination and vocalisation).

2.2. Management post trial

The protocol of the main trial contained no instructions for the pharmacological treatment of cases after completion of the trial, although owners were instructed to continue the behaviour modification implemented during the trial. This approach allowed each investigator to treat each case according to its need, taking into account the preferences of each dog's owner. The owner and the investigator were blind to the pharmacological treatment received during the main study. Thus, decisions regarding drug treatment post trial were made without knowledge of whether clomipramine or placebo had been administered previously. No specific instructions were given to reduce progressively the dose of drugs at cessation of treatment and this information was not recorded.

2.3. Follow-up questionnaire

We attempted to contact all owners of the dogs after the main trial was completed. A standard questionnaire was completed by telephone by either the investigator ($n = 2$ for sites in the US) or trial monitor ($n = 1$ each for the sites in France and UK). Inter-rater reliability was not assessed.

2.4. Statistical analysis

In all cases, the software SAS Online Doc® Version 8, Cary, NC: SAS Institute Inc., 1999, was used. Differences between groups were tested for statistical significance with the Fisher's exact test (SAS® procedure frequency) for frequency data and with ANOVA (SAS® procedure mixed) for numerical data. In all cases, a two-tailed α-level of 0.05 was defined as significant.

3. Results

3.1. Summary results of main trial (King et al., 2000)

A total of 89 dogs were included in the analyses; 26 received standard-dose clomipramine, 33 low dose clomipramine and 30 placebo. The groups were considered matched at baseline.

The signs of anxiety (destruction, defecation, urination and vocalisation) improved in all treatment groups, but the response was greatest in the standard-dose clomipramine

group which produced a higher frequency of improvement or disappearance of the four signs at all time points (days 28, 56 and 84) as compared to placebo. Improvement was significant ($P < 0.05$) for all four signs at either one or two time points. A major benefit of clomipramine as compared to placebo was to produce faster reduction in signs of anxiety. Low dose clomipramine produced greater improvement than placebo for most parameters, but differences between groups did not reach statistical significance.

3.2. Follow-up investigation

Owners of 78 out of 89 dogs were contacted by telephone by an investigator ($n = 2$) or monitor ($n = 2$). Two dogs had died for reasons unrelated to separation anxiety or the treatments administered (one each in the low dose clomipramine and placebo groups). Therefore, useful data were obtained from 76 cases. The investigations were conducted between 5.5 and 16 months after completion of the main trial. A total of 28 dogs (5 in France, 1 in UK, 22 in the US) received some drug therapy at the end of the trial. Data were divided into two categories: (1) dogs that received clomipramine for more than 12 months after completion of the trial; (2) dogs that received either no treatment or a drug treatment for a maximum of seven months after completion of the trial.

3.2.1. Dogs that received clomipramine for more than 12 months

A total of 12 animals at one US site received clomipramine and behavioural therapy at the end of the study and were still being treated with clomipramine, when the follow-up investigation was made 13–16 months after stopping the trial (Table 1). No cases of adverse effects or worsening of behaviour were noted. A further improvement in behaviour was noted in 10 dogs and no change was recorded in the remaining two animals. No differences were observed ($P = 1.0$) between the groups.

3.2.2. Dogs that received either no treatment or treatment for up to seven months

A total of 48 dogs received no drugs, while 16 received drugs for up to seven months after the end of the trial (Table 2). In all cases, drug treatment was stopped at least four months before the follow-up investigation was made. At the US sites, 10 dogs received drugs for between 1 and 30 weeks. The drugs used (no. of dogs) were clomipramine ($n = 10$) for 1–30 weeks, trazodone ($n = 2$) for 9–17 weeks, alprazolam ($n = 3$) for 3–30 weeks and clonazepam ($n = 1$) for 13 weeks. A total of five dogs received clomipramine alone and five received clomipramine in combination with another drug. At the French and UK sites, a total of six dogs received drug therapy for a maximum of 10 weeks. The drugs used (no. of dogs) were clomipramine ($n = 4$) for 4–9 weeks, pipamperone and chlorpromazine ($n = 1$) for 10 weeks, and paroxetine ($n = 1$) for an undefined time.

A total of 52 dogs (90%) continued to receive some form of behavioural therapy after the end of the trial, while only six owners reported discontinuing behavioural therapy.

There were no significant differences between groups in frequencies of pharmacological ($P = 0.48$) or behavioural ($P = 1.0$) therapy in the follow-up phase.

Changes in behaviour after the end of the trial were noted for 25 of 57 dogs for which data are available. These were classified into three groups:

Table 1
Follow-up data from 12 dogs at one site (investigator, K.L. Overall), which received clomipramine long term after the end of main trial

Treatment group in main trial	All groups	1–2 mg/kg, PO, q12h clomipramine	0.5–1 mg/kg, PO, q12h clomipramine	Placebo, PO, q12h	P value
Number of cases included in follow-up	12	4	5	3	
Pharmacological treatment after end of trial					
Treated with clomipramine	12 (100%)	4 (100%)	5 (100%)	3 (100%)	1.0
Treated with other drugs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Behavioural therapy after end of trial					
Received behavioural therapy	12 (100%)	4 (100%)	5 (100%)	3 (100%)	1.0
Change in behaviour after end of trial					
Behaviour worsened from 0 to 2 weeks	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0
Behaviour worsened (>2 weeks)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Behaviour improved (>2 weeks)	10 (83.3%)	3 (75%)	4 (80%)	3 (100%)	
No change in behaviour after trial	2 (16.7%)	1 (25%)	1 (20%)	0 (0%)	

All dogs were still receiving clomipramine at the time of the follow-up at 13–16 months. Data are the number (%) of dogs.

Table 2
Follow-up data from cases that received either no drugs ($n = 48$) or drugs for a maximum of seven months ($n = 16$) at the end of the trial

Treatment group in main trial	All groups	1–2 mg/kg, PO, q12h clomipramine	0.5–1 mg/kg, PO, q12h clomipramine	Placebo, PO, q12h	P value
Total number of cases included in follow-up	64	16	25	23	
Pharmacological treatment after end of trial					
No pharmacological treatment	48 (75%)	11 (68.7%)	17 (68%)	20 (87%)	0.48
Treated with clomipramine alone	9 (14.1%)	4 (25%)	3 (12%)	2 (8.7%)	
Treated with clomipramine + other drug	5 (7.8%)	1 (6.3%)	3 (12%)	1 (4.3%)	
Treated with other drug alone	2 (3.1%)	0 (0%)	2 (8%)	0 (0%)	
Mean (range) duration of treatment with clomipramine (weeks)	14.1 (1–30)	13.6 (1–28)	16.6 (1–30)	10.8 (4–17)	
Behavioural therapy after end of trial					
Received behavioural therapy	52 (89.7%)	13 (92.9%)	20 (90.9%)	19 (86.3%)	1.0
Received no behavioural therapy	6 (10.3%)	1 (7.1%)	2 (9.1%)	3 (13.4%)	
Change in behaviour after end of drug therapy					
Behaviour worsened from 0 to 2 weeks	3 (5.3%)	0 (0%)	3 (15%)	0 (0%)	0.0022
Behaviour worsened (>2 weeks)	10 (17.5%)	2 (13.3%)	3 (15%)	5 (22.7%)	
Behaviour improved (>2 weeks)	12 (21.1%)	7 (46.7%)	5 (25%)	0 (0%)	
No change in behaviour after trial	32 (56.1%)	6 (40%)	9 (45%)	17 (77.3%)	
Mean (range) time to worsening (>2 weeks) (weeks)	17.8 (4–39)	36.9 (34.7–39)	11 (9–13)	10.8 (4.3–26)	0.0074
Signs shown with worsening (>2 weeks)					
Destruction	5	2	1	2	
Defecation/urination	3	0	2	1	
Vocalization	2	0	1	1	
Other	2	0	1	1	

In all cases, a minimum period of four months had elapsed between the cessation of drug therapy and the follow-up. Data are the number (%) of dogs.

(A) Further improvement in behaviour was noted in 12 dogs, all of which had been treated with clomipramine during the trial. A total of seven of these dogs were treated with drugs (six received clomipramine) after the end of the trial, and all cases with a response ($n = 5$) had continued to receive behavioural therapy. The remaining five dogs received no drugs after the end of the trial. Of these cases, two received no further behavioural therapy, while three dogs received behavioural therapy.
(B) Worsening of behaviour in the first two weeks after stopping the trial was noted in three dogs, all of which had been treated with low dose clomipramine during the trial. Behavioural therapy had been continued in two of the cases and stopped in one case. All three dogs showed signs of anxiety immediately after stopping drug therapy at the end of the trial. Signs exhibited were (1) defecation and urination; (2) vocalisation and nervous disposition; (3) reluctance to be left alone plus occasional licking behaviour. After the reaction was noted, one dog was given standard-dose clomipramine and the dose reduced over a period of two weeks. No adverse signs were observed when clomipramine treatment was stopped for the second time in this dog.
(C) Worsening in behaviour that occurred at least two weeks after cessation of clomipramine treatment was reported in 10 of 57 dogs (17.5%). Worsening was reported in 3 of 22 dogs (13.6%) in which signs of anxiety had "disappeared" at the end of the trial, and in 5 of 40 dogs (12.5%) in which signs were still present at the end of the study.

The incidence of worsening was lower in dogs that had received clomipramine during the trial (12.3–15.0%), as compared to the placebo group (22.7%). The time from cessation of drug treatment to the change in behaviour was shorter in the placebo (4, 4.3, 8.7, 13 and 26 weeks) and low dose clomipramine groups (9, 11 and 13 weeks), as compared to standard-dose clomipramine (34.7 and 39 weeks). Differences reached statistical significance using ANOVA, although the group sizes were not equal. P values were $P = 0.0074$ for the overall comparison, and in the post hoc comparisons $P = 0.0033$ (placebo versus standard-dose clomipramine), $P = 0.0050$ (low versus standard-dose clomipramine) and $P = 0.97$ (placebo versus low dose clomipramine). Of the 10 dogs with reported worsening of behaviour, one demonstrated attention-seeking behaviour and another refused to leave the house. The remaining dogs showed signs of anxiety in the owner's absence (destruction, defecation, urination or vocalisation), and in all cases the dogs had shown exactly the same signs before starting the clinical trial.

Differences between groups reached statistical significance ($P = 0.0022$) for the frequencies of changes in behaviour after the end of the trial (worse, improved, no change, Table 2). In the post hoc comparisons, significance was reached for the comparisons standard-dose ($P = 0.0016$) or low dose clomipramine ($P = 0.0074$) versus placebo, but not low dose clomipramine versus placebo ($P = 0.40$).

4. Discussion

The results suggest that there are no short or long term adverse consequences of using standard-dose clomipramine for the management of separation anxiety in dogs. Caution is

urged in the interpretation of the results, however, since the methods used have limitations. The management of the dogs was not standardised after completion of the clinical trial and possible triggers for changes in behaviour post trial were not evaluated. In addition, recall bias is inherent in the results as owners were asked to recall their dog's behaviour, retrospectively. In addition, the assessments were made by four different people and inter-observer reliability was not assessed. However, we do not think this was a significant limitation to the results, since a standard questionnaire with simple-to-understand questions was used in all cases. Although statistical significance was reached for some end points (lower worsening rate and longer time to worsening for standard-dose clomipramine versus placebo), these analyses are not highly robust due to low numbers of cases. Nevertheless, some important conclusions can be drawn from the results of this investigation.

After completion of the main trial, most (91%) dogs continued to receive behavioural therapy. A total of 37% of dogs received drugs after the study, although there was a marked difference between countries and investigators. In the US, many dogs (76%) received drug therapy after the trial. At one US site, 12 dogs were maintained on clomipramine and behavioural therapy for long periods after the study (up to 16 months at the time of questioning). No adverse effects of the drug or return of the signs of separation anxiety were noted and, in fact, many dogs (83%) were reported to have continued to improve. In contrast, only a small number of dogs (13%) at the European sites were maintained on clomipramine or other drugs after the trial for up to three months, while drug therapy was stopped at day 56 or 84, in the majority of cases (87%). These results suggest country- and investigator-specific biases that influence whether or not drugs are utilized or continued.

In both human psychiatry and veterinary behavioural medicine, it is desirable to use drugs for the minimum time necessary. However, relapse rates of conditions such as panic and obsessive–compulsive disorders are common in humans after cessation of therapy, and therefore many patients are maintained on drugs long term (Modigh, 1990; McTavish and Benfield, 1990). Relapse of stereotypies after removal of drugs in dogs is also common (Overall and Dunham, 2002). In our study, no relapses (0%) were recorded in the dogs maintained on clomipramine, while approximately 13% of cases relapsed once therapy had been withdrawn. Nevertheless, a direct comparison of results is not reliable, since different centres were involved. Controlled studies would be needed to evaluate the relative benefits of stopping clomipramine early (e.g. after 2–3 months), as compared to longer courses of treatment in dogs with separation anxiety.

There were no reported cases of acute worsening of the dog's condition immediately after stopping treatment in the standard-dose clomipramine or placebo groups. However, three dogs in the low dose clomipramine group showed worsening of anxiety soon after stopping drug treatment at the end of trial. In humans, relatively rare "withdrawal syndromes" can occur when SSRIs, TCAs and MAOIs are withdrawn suddenly, so it is recommended to reduce the dose of these drugs gradually when stopping therapy (Lejoyeux et al., 1996). Similar recommendations have also been made in veterinary medicine (Hewson and Luescher, 1996; Overall, 2001) and withdrawal signs of trembling, pacing and hiding were reported in a dog after stopping treatment with clomipramine for the treatment of lick granuloma (Hewson et al., 1998). However, if the three cases of worsening of anxiety we observed are analogous to the acute withdrawal syndrome described in humans, it would be expected that dogs treated with standard-dose clomipramine would be equally or more affected than those

treated with the low dose. This was not the case. A total of 11 dogs received standard-dose clomipramine for 56–84 days during the trial and no drug treatment post trial, and no dog experienced acute worsening of anxiety when clomipramine treatment was stopped. A further five cases received standard-dose clomipramine during the trial and received clomipramine post trial for an additional 1–28 weeks, and none of these dogs showed signs when drug therapy was stopped. Therefore, we consider it probable that the worsening anxiety noted in three dogs after withdrawal of low dose clomipramine was most likely to have been a relapse of the original anxiety disorder, which had not been controlled adequately, rather than being due to withdrawal of the drug per se. No adverse events were noted after sudden withdrawal of clomipramine treatment for six months to healthy dogs at dosages ranging from 4 to 20 mg/kg, PO, q24h (J.N. King, unpublished data). The results of our study do not indicate that withdrawal of standard-dose clomipramine poses a risk. However, caution may be needed with sudden cessation of low doses of clomipramine (0.5–1 mg/kg, PO, q12h), notably if signs of anxiety have not been controlled fully.

After cessation of therapy with clomipramine or placebo, 10 dogs (17.5%) showed worsening of behaviour in the following 4–39 weeks. Of these 10 cases, nine showed the same signs of separation anxiety presented before the start of the trial. Of these nine dogs, three had no signs of anxiety at the end of the trial and were therefore rated as treatment successes. The remaining six dogs did not have complete resolution of signs of anxiety by the end of the trial. Accordingly, calculation of a "relapse rate" is problematic. In the 12 dogs that continued to receive clomipramine long term, the worsening rate was 0%. In the dogs in which therapy with standard-dose clomipramine was stopped, 2 of 15 animals (13%) showed worsening signs of separation anxiety after stopping drug therapy. Of all dogs treated (either dose of clomipramine or placebo), 10 of 57 cases (17.5%) showed worsening signs of separation anxiety after stopping drug therapy. Not all of these cases had full resolution of signs of anxiety at the end of trial however, the "relapse rate" of cases that had no signs of separation anxiety at the end of the trial was 13.6% (3 of 22 dogs).

The behaviour of 12 dogs (20%) improved further after the end of the trial and interestingly all of these cases had received clomipramine during the study. Dogs that had received standard-dose clomipramine during the trial more frequently further improved (47%), less frequently worsened (13%) and had a longer time to worsening (37 weeks) as compared to dogs that had received placebo (0%, 23% and 11 weeks, respectively). Differences reached statistical significance from placebo ($P \leq 0.003$), although the analyses are not highly reliable, since the number of cases is low. Nevertheless, the results raise the possibility that dogs receiving clomipramine in addition to behavioural therapy might have a higher chance of permanent control of separation anxiety as compared with dogs that receive only behavioural therapy. A mechanistic rationale for this result is plausible if clomipramine had a synergistic effect in improving the efficacy of the behavioural therapy. Effects of clomipramine on memory and learning in humans are beneficial in some situations but negative in others (Bartfai et al., 1991; Kim et al., 2002). Any "long term" benefit of clomipramine in improving the ability of dogs to learn new behaviours would be an addition to its proven "short term" effect of reducing signs of separation anxiety during treatment (King et al., 2000). These observations merit testing.

5. Conclusions

No adverse effects were reported after withdrawal of standard-dose clomipramine (1–2 mg/kg, PO, q12h) for the treatment of dogs with separation anxiety. It has been shown previously that clomipramine reduces the signs of separation anxiety in dogs while it is being administered (King et al., 2000). The possible long term benefit of clomipramine treatment in reducing the frequency and/or increasing the time to relapse of separation anxiety merits further testing.

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