Comparison of the efficacy of a synthetic dog-appeasing pheromone with clomipramine for the treatment of separation-related disorders in dogs

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Sixty-seven dogs that showed signs of distress when separated from their owners (destructiveness, excessive vocalisation and house soiling) and hyperattachment were used in a randomised, blind trial to assess the potential value of a dog-appeasing pheromone in reducing the unacceptable behaviours. For ethical reasons, there was no placebo group and the effects of the pheromone were compared with the effects of clomipramine which is regularly used to treat this type of problem. The undesirable behaviours decreased in both groups, but the overall assessment by the owners indicated that there was no significant difference between the two treatments, although there were fewer undesirable events in the dogs treated with the pheromone, and the administration of the pheromone appeared to be more convenient.

SEPARATION-RELATED behaviour problems in dogs occur only when the dog is separated from or denied access to its owner. Typically, the main complaints are destructiveness, excessive vocalisation and house soiling, but some dogs may hyperventilate, vomit, salivate, urinate or have diarrhoea. Several causes have been suggested (Voith and Borchelt 1985, McCrave 1991, Overall and others 1999, Takeuchi and others 2000). Until recently, the term 'separation anxiety' was used as a synonym for 'separation-related behaviour problems' (Heath 2002), but it is now recommended that the term is used only to describe dogs with undesirable behaviours motivated by anxiety (Appleby and Pluijmakers 2003). In 1982, Borchelt and Voith proposed that one explanation for this problem was the strong social bond between the dog and its owner, and other authors have described the signs of a strong attachment between some dogs and their owners; for example, they may follow the owner from room to room (McCrave 1991), they may avoid being left alone in a room (McBride and others 1995) and they may sleep close to the owner (Jagoe and Serpell 1995). The terms 'hyperattachment' and 'overattachment' are used by some authors to describe these excessive contact-seeking behaviours (Pageat 1995, Takeuchi and others 2000, Flannigan and Dodman 2001, Appleby and Pluijmakers 2003). Behavioural data have shown that the typical signs of hyperattachment are strongly correlated with the signs of distress in dogs suffering from separation-related behaviour problems (Gaultier 2001). It is necessary to consider the dog's behavioural signs carefully to determine an accurate causal diagnosis; otherwise, any proposed treatment may focus only on the disruptive behaviours, and the distress underlying these behaviours may remain untreated (McCrave 1991, Pageat 1995).

Separation-related behaviour problems are the second most common behavioural disorder recorded in dogs at referral behavioural practices, coming just after aggression (Borchelt and Voith 1982, Wright and Nesselrote 1987, Landsberg 1991, McCrave 1991, Pageat 1995, Overall 1997, Simpson 2000, Gaultier 2001). The consequences of house soiling and destructiveness on the home and the effects of vocalisation on the neighbourhood often upset owners and may lead them to surrender their dog to a shelter if a quick solution is not found (Van der Borg and others 1991, Lesaine 1996). Most of the undesirable behaviours are also significant in terms of the dog's own welfare, and relieving the distress of affected dogs should therefore be a priority.

There are now many behavioural plans and pharmacological treatments which appear to be effective (Tuber and others 1982, Pageat 1995, O'Farrell 1997, Overall 1997, Podberscek and others 1999, Blackwell and others 2002). Among these protocols, only the use of behavioural therapy combined with clomipramine (a psychotropic drug which is a combined serotonin and noradrenalin reuptake inhibitor) has been formally validated in randomised, placebo-controlled studies (Petit and others 1999, Podberscek and others 1999, King and others 2000). This combination will be referred to as the 'reference treatment'. It has been shown that the reference treatment increases the rate at which dogs improve or resolve (63 per cent from day 28 onwards) in comparison with dogs treated by a behaviour modification plan alone (29 per cent) (King and others 2000). But drugs may have drawbacks, including undesirable side effects, and they may be difficult to administer regularly; these drawbacks can be a real obstacle to maximal compliance.

A group of pheromones, secreted in the mammary area shortly after parturition, was first identified by Pageat (2000). Because these pheromones seem to have an appeasing effect on both young and adult animals they were called 'appeasines' (Pageat and Gaultier 2003). Dog-appeasing pheromone (DAP; Ceva Santé Animale) is a synthetic analogue of this mixture of esters of fatty acids produced by the sebaceous glands in the intermammary sulcus of bitches. It can be delivered by means of an electric diffuser (Shepperd and Mills 2003).

A placebo-controlled trial may be considered unethical in accordance with the recent guidance on statistical principles for trials (Anon 1999). In this case, the synthetic pheromone was compared with clomipramine, the efficacy of which has been established in well designed trials by Petit and others (1999) and King and others (2000).

MATERIALS AND METHODS

Type of comparison

The lack of any placebo group makes external validation necessary. To this end, the active control trial should have the same design features (primary variables, dose of active comparator, eligibility criteria, and so on) as previously conducted superiority trials (Anon 1999, Steinijans and others 2000). The chi-squared test and Mann-Whitney U test have been used to analyse secondary parameters. The secondary

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parameters assessing efficacy were analysed on the results from the animals which fulfilled the full protocol, and the other secondary parameters (demographic differences and tolerability) were analysed on the results from all the dogs.

Recruitment of subjects

The dogs were recruited at veterinary clinics in France, Italy, Spain and Switzerland, all of which had a significant behavioural referral case load, and the selection criteria were similar to those applied in the trials by Petit and others (1999) and King and others (2000) (Table 1). The dogs were recruited after a behavioural examination, in order to exclude dogs with organic medical problems, and after a detailed behavioural questionnaire assessed by the veterinarian. If the dog fulfilled the criteria, it was randomly assigned to a treatment group, and after having obtained the written consent of the dog's owner, the behavioural modification plan – the same as that in the trials by Petit and others (1999) and King and others (2000) – was presented to the owner.

Treatments

The dogs were assigned to the two treatment groups at random. The pheromone was administered through a reservoir-type electrical diffuser, containing 30 ± 0·2 g of a 2 per cent solution of the synthetic pheromone in paraffin oil. Ideally, the diffuser had to be installed in the room in which the dog tended to spend most of its time during the day, and to which it had access in the absence of its owners. If this was not possible it had to be installed in a part of the house in which the dog was allowed to remain when its owner was absent. Clomipramine was administered orally twice a day in capsules supplying 1·0 to up to 2·0 mg/kg bodyweight, equivalent to between 2 and 4 mg/kg/day. Each capsule contained equal parts of a mixture of clomipramine hydrochloride and medicinal grade lactose. A placebo diffuser, containing a mixture of two mineral oils chemically similar to those used for the pheromone solution, was installed in the houses of the dogs receiving clomipramine, to preserve the blind nature of the trial. The dogs in the pheromone group similarly received placebo capsules containing only lactose. The random assignments of the treatments were balanced every six cases by each investigator. Any other kind of treatment that could modify the behaviour of the dog or its gastrointestinal and urinary functions was forbidden during the trial.

Trial period

The treatments were administered for a mean period of 28 days (with a minimum of 24 days and a maximum of 33 days). This period was chosen for two main reasons. First, owners with a problem dog often ask for a quick improvement, and to be considered a relevant therapy any product must therefore be effective in a short period and one month was believed to meet this requirement. Secondly, the new treatment should be assessed under conditions in which the reference treatment shows its highest possible efficacy (Garbe and others 1993, Anon 1999), and clomipramine reached its highest efficacy after 28 days (King and others 2000). The dogs were seen by the investigator for a veterinary and behavioural examination on the day the treatment began (visit 1, day 0) and 28 days later (visit 3). The owners were contacted by telephone by the vet between day 12 and day 18, the day of the second visit (visit 2).

Assessment criteria

Efficacy The overall efficacy of each protocol was assessed on the basis of a variable integrating the owner's and the vet's overall impression about the change in the state of the dog; it therefore took into consideration not only the signs shown during the owner's absence but also the behaviour of the dog when its owner was present. The variable was a scale of ordered ratings of the change in the dog's overall behaviour between visit 2 or 3 and visit 1, in which the categories were 'worse', 'no change', 'reduced' and 'disappeared'. The primary target signs shown during the owner's absence were 'destruction', 'vocalisation' and 'house soiling', and they were rated as 'worse', 'no change', 'reduced', 'disappeared' or 'newly appeared', as compared with the baseline visit on day 0. 'Disappeared' was defined as the total absence of the sign since the last visit, 'newly appeared' as the appearance of the sign since the last visit, 'worse' and 'reduced' were based on changes in the frequency of the behaviour. Taking into account the response of the owners to specific questions and the daily monitoring form, the results were recorded and compiled by the investigator. The monitoring form indicated how many times and for how long the owner had been absent on each day, and what the dog had done, in terms of destruction, vocalisation and house soiling, during their absence. This information helped the investigator to improve the objectivity of the overall assessment of efficacy.

The investigator also took into consideration 'secondary signs of distress', including sleeping problems, excessive licking, feeding and drinking problems, gastrointestinal problems and other behaviours such as over-reaction to stimuli, lack of adaptation to changes, and reduced exploratory behaviour, signs which could be evaluated objectively. Some of these signs were shown not only in the absence but also in the presence of the owner. They were rated as either 'present' or 'absent' at each visit.

Tolerability The tolerability of the two treatments was evaluated by questioning the owner by phone at visit 2 and directly at visit 3, and completed by a behavioural examination of the dog at visit 3. The frequency and severity of each adverse sign was recorded.

Compliance At the beginning of the protocol, the investigator gave the owner the bottles containing the number of capsules needed for the full treatment, that is 30 days plus three days to cover unforeseen eventualities, and a diffuser containing 30 ± 0·2 g of DAP solution. For the clomipramine treatment, compliance was assessed by comparing the number of capsules returned, and hence the number administered, with the number required for the effective duration of the treatment. For the DAP therapy, compliance was assessed by comparing the weight of the solution vaporised with the effective duration of the treatment.

Statistical analysis

The Hauck-Anderson corrected classical procedure for independent binary endpoints (Tu 1997) was used to assess the one-way confidence in the treatment.

The statistical analysis used in non-inferiority trials is very specific; its main characteristic is to specify a lower equiva-

TABLE 1: Numbers of dogs that failed to adhere to the full protocol, and the reasons for their exclusion, and the numbers that did adhere to the full protocol

Category	Number of dogs	Treatment		Reason for exclusion
		Clomipramine	DAP	
Excluded from full protocol	10	1	1	Loss of follow up before any control visit
		0	1	Loss of follow up after the first control visit
		0	1	Withdrawal of owner consent
		1	0	Other medical event
		0	1	Other non-medical event
		0	1	Breaking of blinding code after the first control visit
		2	2	Lack of efficacy
Full protocol	57	27	30	

DAP Dog-appeasing pheromone

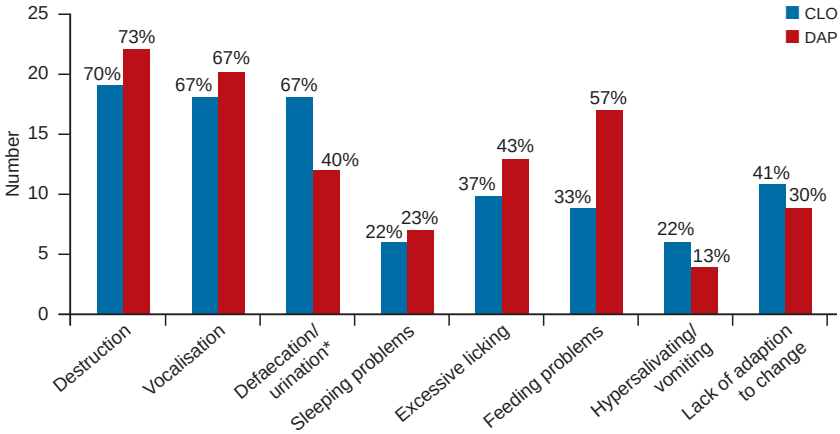

FIG 1: Numbers and percentages of the 57 dogs treated for 28 days with either clomipramine (CLO) or dog-appeasing pheromone (DAP) which showed particular behavioural signs when they were separated from their owners. * Significant difference, P<0·05

TABLE 2: Sex, breed and mean, median and ranges of the ages and weights of the 31 dogs treated with clomipramine and the 36 dogs treated with dog-appeasing pheromone (DAP)

Variable	Treatment: Clomipramine	Treatment: DAP
Age (years)		
Mean	2·81	2·82
Median	1·5	1·5
Range	0·65–9·0	0·55–13
Sex		
Male	13 (42%)	20 (56%)
Neutered	3	1
Entire	10	19
Female	18 (58%)	16 (44%)
Neutered	6	4
Entire	12	12
Weight (kg)		
Mean	17·5	17·3
Median	16	15·5
Range	5–35·5	4–39·1
Breed		
Pure breed	20 (65%)	24 (67%)
Mixed breed	11	12

lence margin. This margin 'd' is the largest difference that can be judged as being behaviourally acceptable and should be smaller than the difference observed in superiority trials of the active comparator (Anon 1999). When there is no consensus in the field of the problem, the value of d is arbitrarily determined as 0·2 (relative value) (Com-Nougue and Rodary 1987, Bristol 1999). So, hypothesising that DAP should be better tolerated and easier to administer, the two protocols would be considered for these practical purposes to be equivalent if the DAP efficacy results are unlikely to be more than 20 per cent less than the reference treatment results.

For the primary variable (the overall assessment), 'disappeared' and 'reduced' cases were rated as 'success', and 'worse' and 'no change' as 'failure'. For all the other parameters, a classical non-superiority approach was used. Qualitative variables assessing destruction, vocalisation, house soiling and secondary signs of distress were tested with a two-tailed chi-squared test with P<0·05 considered significant.

TABLE 3: Global assessments of the effectiveness of the two treatments on the behaviour of the 57 dogs which adhered to the full protocol and on the behaviour of all 67 dogs

Category	Effect on abnormal behaviour: No change (%)	Reduced (%)	Disappeared (%)	Reduced + disappeared (%)	Total
Full protocol					
CLO	8 (30)	13 (48)	6 (22)	19 (70)	27
DAP	5 (17)	20 (66)	5 (17)	25 (83)	30
All the dogs					
CLO	10 (32)	15 (49)	6 (19)	21 (68)	31
DAP	9 (25)	22 (61)	5 (14)	27 (75)	36

CLO Clomipramine, DAP Dog-appeasing pheromone

TABLE 4: Effects of treatment with clomipramine (CLO) or dog-appeasing pheromone (DAP) for 28 days on the main separation-related disorders in the dogs

Treatment	Behaviour	Worse (%)	No change (%)	Reduced (%)	Disappeared (%)	Reduced + disappeared (%)	Total
CLO	Destruction	0	5 (25)	8 (40)	7 (35)	15 (75)	20
	Defaecation/ urination	0	2 (12)	6 (29)	10 (56)	16 (89)	18
	Vocalisation	2 (11)	2 (11)	9 (50)	5 (28)	14 (78)	18
DAP	Destruction	0	2 (9)	7 (32)	13 (63)	20 (91)	22
	Defaecation/ urination	0	3 (25)	5 (42)	4 (33)	9 (75)	12
	Vocalisation	0	7 (35)	8 (40)	5 (25)	13 (65)	20

RESULTS

Twelve centres participated in the study, nine were in France, one in Italy, one in Spain and one in Switzerland. In total 67 cases were randomised and included in the baseline demographic data and in the assessment of tolerability. Of these, 57 cases received the full protocol correctly and were included in the analysis of efficacy (Table 1).

Demographic characteristics and baseline data

The demographic characteristics of the 67 dogs are shown in Table 2; there were no significant differences between the two groups.

The frequencies of the separation-related behaviours shown by the 57 dogs which adhered to the full protocol are illustrated in Fig 1. The most common signs included: destruction (72 per cent), barking (67 per cent), defaecation/urination (53 per cent), feeding problems (46 per cent), excessive licking (40 per cent), lack of adaptation to change (35 per cent), sleeping problems (23 per cent) and hypersalivation/vomiting (17·5 per cent); too few dogs showed this last behavioural sign to allow statistical analysis. Most of the signs were well balanced between the two groups except for defaecation/urination and feeding problems; there were significantly more dogs in the clomipramine treatment group with defaecation/urination problems (P<0·05), and more dogs in the DAP group with feeding problems, but the difference did not reach significance. In the clomipramine treatment group the problem had been present, on average, for 1·7 years (range one month to eight years), and in the DAP group for 1·5 years (range one month to six-and-a-half years).

Assessment of efficacy

The results of the global assessment by the owners of the main parameters chosen to assess efficacy are shown in Table 3. Equivalence testing for independent binary endpoints via the Hauck-Anderson corrected classical procedure (Tu 1997) fixed the lower range for the dogs which adhered to the protocol at –0·08 and for all the dogs at –0·13. These two results are within the specified limit of –0·2, indicating that the DAP treatment was not inferior to the clomipramine treatment. The results for each particular behavioural sign are shown in Tables 4 and 5. There were no significant differences between the two groups.

The results for the secondary distress signs (Table 5) were also not significantly different between the two groups. Both

TABLE 5: Results of treatment with clomipramine (CLO) or dog-appeasing pheromone (DAP) for 28 days on the dogs which showed secondary signs of separation-related disorders

Treatment	Sleeping problem (%) Day 0	Sleeping problem (%) Day 28	Self-licking (%) Day 0	Self-licking (%) Day 28	Feeding problem (%) Day 0	Feeding problem (%) Day 28	Hypersalivating/ vomiting (%) Day 0	Hypersalivating/ vomiting (%) Day 28	Lack of adaptation to change (%) Day 0	Lack of adaptation to change (%) Day 28
CLO	6	0	10	5 (50)	9	4 (44)	6	1 (17)	11	4 (36)
DAP	5	2 (29)	13	5 (38)	7	9 (53)	4	2 (50)	9	3 (33)

treatments greatly reduced sleeping problems and improved the other signs by more than 50 per cent.

Two dogs in each treatment group were withdrawn before day 28 owing to a lack of efficacy. In the clomipramine treatment group one dog was withdrawn before day 14 because its diarrhoea did not decrease, and the other was withdrawn after day 14 because it ate part of the electricity supply and set the house on fire; the owners of both these dogs requested that they be euthanased. In the DAP group one dog was withdrawn before day 14 because its owner complained of systematic vomiting after the administration of the placebo pills; the second dog was withdrawn after day 14 because the owner's neighbour lodged a complaint against him because the dog vocalised too much and the DAP treatment had not reduced the problem. The owner gave the dog to a member of his family because its problems of destruction and urination were rated as 'disappeared' and 'reduced' respectively.

Assessment of tolerability

The frequencies of reported undesirable behaviours are shown in Table 6, regardless of their severity or the duration of the treatment. Significantly more of the dogs in the clomipramine treatment group showed undesirable behaviours ($P<0.005$); gastrointestinal problems affected seven dogs, changes in appetite affected six and two dogs were lethargic. In the DAP group no particular undesirable behaviour was more common than the others. Four of the dogs in the clomipramine treatment group and one in the DAP group had many episodes of vomiting immediately after the treatment was administered; they may have been related to the method of administration rather than to the treatment itself. When these cases were excluded from the analysis, there were still significantly more of the dogs in the clomipramine treatment group which showed undesirable behaviours ($P<0.05$).

One dog in the DAP group showed aggressive behaviour at the end of the trial although it had had no previous history of aggressive behaviour. Complementary questioning revealed the appearance of typical signs of dominance and territorial aggression; all these signs disappeared after two weeks of a behavioural plan for dominance aggression. One dog in the DAP group showed signs of discomfort and fear micturition at the beginning of the treatment every time the owner returned home. At visit 2 (phone contact) it appeared to the vet that the behavioural plan was being applied too enthusiastically. After further explanation of some points of the protocol, the owner changed his attitude towards his dog and the signs disappeared from day 15 to the end of the treatment.

TABLE 6: Numbers of dogs which showed undesirable behaviours while being treated for 28 days with clomipramine (CLO) or dog-appeasing pheromone (DAP)

Undesirable behaviour	Treatment CLO	Treatment DAP
Gastrointestinal signs/appetite		
Intermittent vomiting/gastritis	1	1
Vomiting just after administration	4	1
Intermittent diarrhoea/colitis	2	0
Anorexia/weight loss	3	1
Increased appetite/weight gain	3	1
Constipation	1	0
Hypersalivation	1	1
Neurological signs		
Lethargy/sleepiness	2	1
Trembling/discomfort	0	1
Aggression	0	1
Hyperactivity crisis	2	0
Other medical conditions		
Fear micturition	0	1
Total	19	9*

* Significant difference ($P<0.05$)

Assessment of compliance

Only 18 of the owners of the dogs on the clomipramine treatment adhered to the protocol perfectly, but in the other cases the compliance was better than 80 per cent. In the DAP group two owners maintained the treatment for less than 50 per cent of the prescribed time, but the others maintained it for more than 80 per cent of the time. In more than 97 per cent of the cases the weight of the solution vaporised was equal to the theoretical value.

DISCUSSION

The results of this trial indicate that DAP, in combination with a behavioural plan, can quickly reduce the undesirable behaviours exhibited by dogs suffering from separation-related problems and overattachment. There was a marked decrease in the main behavioural signs of destruction, vocalisation and urination/defaecation, and also in the secondary distress signs of excessive licking, sleeping and feeding problems, and gastrointestinal disorders. The results produced by DAP were similar to those produced by the reference treatment, clomipramine, but although its efficacy appeared to be the same, the treatment with DAP had practical benefits: undesirable effects were reported less frequently and the simple form of administration potentially increased the compliance to the overall protocol.

The statistical methods used made it possible to draw the conclusion that the DAP treatment was not inferior to clomipramine, rather than that the two treatments were not significantly different in efficacy, a conclusion which is less open to misinterpretation (Com-Nougue and Rodary 1987, Garbe and others 1993, Bristol 1999, Steinijans and others 2000, Chrisley and Reid 2003). However, three methodological aspects had to be observed in order to use this approach. First, the design features which applied to the previous study of the reference molecule were adopted in order to make up for the lack of internal validity; secondly, the behavioural acceptance range followed the guidelines (US Food and Drug Administration 1992, Anon 1999) and corresponded to the arbitrary margin proposed in the literature (Com-Nougue and Rodary 1987); thirdly, the data from both the dogs which met the conditions of the protocol in full, and all the dogs, were analysed.

The demographic data show that the groups treated with DAP and clomipramine were not significantly different in terms of the distributions of dogs of different sex, age and

breed. The demographic data were also similar to those of the dogs in the reference study, except for sex. In the reference study two-thirds of the dogs were male, whereas in this study only half of the dogs were male, but the difference was not significant (King and others 2000). In the reference trial the percentage of neutered dogs of both sexes was significantly greater. Data from a previous study (Gaultier 2001) suggest that this difference is probably linked to local habits and not to a selection bias: dogs are less likely to be neutered in the countries of central and southern Europe than in northern Europe and North America.

The inclusion criteria were strict, particularly the requirement that the dog initially showed signs of hyperattachment. This criterion was applied for two reasons. First, because the new trial was designed to have the same entry criteria as the reference trials, and secondly, because recent data have shown that there is a qualitative difference between dogs showing separation-related problems and hyperattachment and those showing separation-related problems but not hyperattachment (Gaultier 2001), as had been suggested by some authors in the field of pet behaviour (Voith and Borchelt 1985, McCrave 1991, Pageat 1995). Thus, it is important to recognise that the dogs investigated were not representative of all dogs with separation-related problems but only of dogs with both separation-related problems and hyperattachment. The fact that all the dogs showed signs of hyperattachment is important because, according to King and others (2000), it was probably one of the main reasons for the relative failure to demonstrate a benefit of clomipramine in the trial in the UK by Podberscek and others (1999).

The proportions of dogs behaving destructively, vocalising and house-soiling, were respectively 72, 67 and 53 per cent, and similar to the proportions observed in the reference study (73, 71 and 45 per cent) (King and others 2000) and to data in the literature (Petit and others 1999, Gaultier 2001). The proportions of dogs in which these behaviours were 'reduced' or 'disappeared' by the clomipramine treatment in this study were, respectively, 75, 89 and 78 per cent compared with 81, 77 and 58 per cent in the reference trial. These unwanted behaviours occurred in the same proportion in the two treatment groups except for urination/defaecation, which, at the beginning of the trial, affected a much higher proportion of the dogs to be treated with clomipramine. As a result, care is required in evaluating the results of the trial for this behaviour. The results indicated that the clomipramine treatment was more effective than DAP, although the difference was not statistically significant. This result might be expected on the basis of the drug's pharmacological action; it should decrease defaecation and urination by the combined effect of its peripheral anti-cholinergic action (Balant-Gorgia and others 1980, Benfield and others 1991) and its central anxiolytic action. Vocalisation was the behaviour that the two protocols were least effective in reducing.

The results indicate that both treatments were effective in reducing secondary signs of distress. Clomipramine appeared to be excellent for treating sleeping problems and hypersalivation/vomiting; this last result could have been expected on the basis of the drug's peripheral anti-cholinergic action and its 5-hydroxy tryptamine reuptake inhibitor action. The results obtained with DAP were also good, with between 50 to 70 per cent success, but it appeared to be less effective than clomipramine. However, the small number of cases prevented any statistical analysis and any definitive conclusion in comparing the two treatments. Both treatments were successful in nearly half the dogs with feeding problems, but the initial difference between the proportions of dogs with these problems made it impossible to draw any firm conclusion. In previous trials clomipramine had shown evidence of being effective for treating canine acral lick dermatitis (Goldberger and Rapoport 1991, Mertens and Dodman 1996), and the rapid and substantial decrease in self-licking observed in the dogs treated with clomipramine provided further evidence of its value; the DAP treatment gave similar results, with potentially more cases rated as a success. Both products induced great improvements in the dogs' ability to adapt to variations in the environment, indicating that DAP should be useful in situations inducing fear. This result is consistent with a previous study of the effect of DAP on the behaviour of dogs fearful of fireworks (Sheppard and Mills 2003).

This is the first controlled study of the use of DAP together with a behavioural plan in the treatment of dogs with separation-related problems and hyperattachment. The results showed that it reduced many of the problem behaviours. Furthermore, the pheromone did not appear to induce the commonly reported undesirable side effects inherent in the use of drugs, and its convenient form of administration increases the likelihood of owners' compliance.

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