



Fluoxetine combined with clorazepate dipotassium and behaviour modification for treatment of anxiety-related disorders in dogs



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ABSTRACT

The effectiveness of clorazepate dipotassium combined with fluoxetine and a behaviour modification programme for the treatment of anxiety disorders in dogs was investigated. Forty dogs with anxiety disorders were initially enrolled and 36 dogs completed the trial. Dogs were classified into two behavioural categories (anxious dogs with aggression and anxious dogs without aggression) according to their presenting complaints, and were also subdivided into males, females, juveniles and adults. The dog owners were provided with a behaviour modification plan for their dogs to be commenced in the first week of therapy. Clorazepate dipotassium was administered PO at 1.0 mg/kg every 24 h for 4 weeks, and fluoxetine was administered PO at 1.0 mg/kg every 24 h for 10 weeks. Therapy with both drugs was initiated simultaneously. Improvement was reported in 25/36 dogs. Significant differences in treatment effects were observed between anxious dogs with aggression and anxious dogs without aggression ($P < 0.05$). Positive correlations between owner compliance with the treatment plan and reported improvement achieved during three periods of study were also noted.

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Introduction

Dogs are subject to anxiety-related conditions, including aggression, separation anxiety, generalised anxiety, fears and phobias, and compulsive disorders (CD; Overall, 1997, 2001). Extreme fear reactions to noises can predispose dogs to anxiety states, such as phobias (Casey, 2006). In addition, anxious dogs can become irritable and aggressive (Pageat, 1998; Reisner, 2006).

Anxiety and other emotional states that exacerbate certain forms of aggression can be amenable to psychopharmacological intervention (Guy et al., 2001; Landsberg et al., 2003; Mertens, 2006). Anxious animals might require temporary treatment with anti-anxiety drugs so that they can benefit from behaviour modification, since behaviour modification requires learning (Reisner, 2006), which can be inhibited by anxiety (Klein and Evans, 1989). For anxiety disorders, the concomitant use of behavioural therapy and psychotropic drugs yields the most favourable outcome (Hart and Cooper, 1996).

Some types of psychotropic drugs reduce the frequency and severity of behavioural disorders by selectively increasing serotonin concentrations (Fuller, 1996). For example, the serotonin reuptake inhibitor fluoxetine is the drug of choice in some cases of canine behavioural disorders (Simpson et al., 2007; Landsberg et al., 2008). In addition, knowledge derived from medical psycho-

pharmacology can be applied to the task of treating disturbed and undesirable behaviour in dogs, although a cautious approach should be taken and, generally speaking, medications should be used only to complement behaviour modification (Mugford, 2002).

Benzodiazepines are commonly used in the treatment of anxiety (Overall, 1997). Clorazepate dipotassium has been used in dogs when an immediate, short acting effect is required, such as for the treatment of separation anxiety, fears and phobias (Crowell-Davis and Murray, 2006). The elimination half-life of clorazepate dipotassium is approximately 9 h in dogs; treatment should begin at a low dose and can then be increased to effect. In dogs with anxiety disorders, benzodiazepines have been administered in combination with antidepressants; the benzodiazepine controls anxiety until the antidepressant has had enough time to achieve its therapeutic anxiolytic effect. The immediate action of clorazepate dipotassium makes it useful for treating behaviour disorders in anxious animals (Crowell-Davis et al., 2003; Crowell-Davis and Murray, 2006).

Antidepressants effectively control signs of CD, separation anxiety and noise phobia in dogs when used in combination with behaviour modification (Seskel and Lindeman, 2001). It is important to establish a therapeutic plan, together with the dog owner, to discuss what can be expected from a combination of psychoactive drugs and behaviour modification (Crowell-Davis and Murray, 2006; Ibáñez and Anzola, 2009).

Due to the rapid effect of clorazepate dipotassium, we suspected that better compliance with a therapeutic plan could be

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achieved if clorazepate dipotassium was used in combination with fluoxetine, which does not produce its full anxiolytic effect until 4–5 weeks after initiation of therapy (Dodman and Shuster, 2000). In this study, we evaluated the effect of the combination of fluoxetine with clorazepate dipotassium and behaviour modification on the treatment of anxiety disorders in dogs.

Materials and methods

Animals

Thirty-six dogs diagnosed with a variety of behavioural disorders were included in the study (Table 1), comprising 13 females and 23 males (all intact), aged 8 months to 7 years and representing 29 different breeds and seven crossbreeds. All were in good physical condition. The dogs were evaluated at the Animal Behaviour Clinic of the Universidad Complutense de Madrid, Spain. Clinical histories were obtained with a standardised questionnaire (Overall, 1997). Dogs were included in the study if anxiety-related disorders were confirmed by a behavioural history (e.g. signs of restlessness, hyperactivity, extreme attachment causing anxiety during the owner's absence, aggression, lack of attention, nervousness, trembling). Dogs were excluded if they showed other clinical signs, were pregnant, or had received any psychopharmacological treatment in the previous 4 weeks.

All animal procedures followed European and Spanish national legislation on animal protection (Directive 86/609/EEC, Real Decreto 1201/2005). All dog owners were informed about the study and agreed to participate.

A variety of disorders were represented among the enrolled dogs, including aggression (fear aggression, dominance aggression, food-related aggression and inter-dog aggression), separation anxiety, generalised anxiety, fear or phobia and CD. All dogs also showed at least one sign of anxiety, including muscle tension exhibited through certain body postures, excessive vocalisation, nervousness, fearfulness, escape responses or a tendency to hide from certain stimuli and a constant state of alertness. For statistical analysis, dogs were grouped into two behavioural categories according to the primary presenting complaint: aggressive dogs (showing anxiety states with aggression, $n = 12$) and non-aggressive dogs (showing anxiety states

without aggression, $n = 24$). The 36 dogs were also divided into two groups by age (juveniles <3 years, $n = 20$; adults ≥ 3 years, $n = 16$) and two groups by sex (13 females; 23 males).

Behaviour modification plan

We used a behaviour modification plan (Ibáñez and Anzola, 2009) commencing on the first day of the behavioural evaluation, in combination with fluoxetine hydrochloride and clorazepate dipotassium for the treatment of anxiety. The plan comprised three complementary stages that were designed to stop undesirable behaviours and reward desired behaviours that were incompatible with the performance of undesirable behaviours. In stage 1, dog owners were asked to cease even unintentional reward for the undesirable behaviours. In stage 2 (behaviour modification therapy application), dog owners were asked to follow a passive behaviour modification programme designed to teach the dogs to sit quietly, look at the person from whom they were seeking attention, or with whom the interaction was occurring, and wait for the cues for the appropriate behaviour. The dogs received basic obedience training to increase their confidence and enhance communication between dog and owner. The modification plan included the following: (1) rewarding relaxed behaviour only; (2) eliminating the reinforcement of anxious behaviours by reassuring or patting the dog when it showed clinical signs of fear or anxiety; (3) setting a routine for feeding and playing times; and (4) spending 20 min per day in four sessions (5 min each) playing or otherwise actively interacting with the dog. In stage 3, owners were requested to begin active behaviour modification designed to teach the dogs to relax when they would otherwise be engaged in the problem behaviour; in exchange, the dog was given a food or play reward (Overall, 2001).

Pharmacological treatment

Physical and laboratory evaluations were carried out on all dogs before treatment. The dogs received clorazepate dipotassium PO at 1.0 mg/kg every 24 h for 4 weeks (Dodman and Shuster, 2000; Overall, 2001) as an adjunct to fluoxetine, which was administered PO at 1.0 mg/kg every 24 h for 10 weeks. The drugs were commenced simultaneously.

Table 1
Clinical details of 36 dogs treated for anxiety states.

Case	Sex	Age (months)	Primary presenting complaint	Disorder class	Behavioural category
1	M	12	Vocalisation, destructive	SA	Not aggressive
2	M	40	Aggressive	AGG	Aggressive
3	F	12	Nervousness, IE	GA	Not aggressive
4	M	13	Nervousness, noises fear	NPh	Not aggressive
5	F	20	Vocalisation, IE	SA	Not aggressive
6	M	14	Aggressive	AGG	Aggressive
7	F	36	Vocalisation, destructive	SA	Not aggressive
8	M	12	Nervousness, destructive	GA	Not aggressive
9	M	15	Aggressive	AGG	Aggressive
10	M	24	Destructive, nervousness, vocalisation	SA	Not aggressive
11	M	42	Destructive, nervousness	GA	Not aggressive
12	F	24	Vocalisation, destructive	SA	Not aggressive
13	M	8	Aggressive	AGG	Aggressive
14	M	14	Destructive, vocalisation	SA	Not aggressive
15	M	12	Nervousness	GA	Not aggressive
16	M	18	Vocalisation	GA	Not aggressive
17	M	12	Destructive, vocalisation	SA	Not aggressive
18	M	36	Nervousness, destructive	GA	Not aggressive
19	M	36	Aggressive	AGG	Aggressive
20	M	44	Aggressive	AGG	Aggressive
21	M	15	Aggressive	AGG	Aggressive
22	F	54	Circling	OCD	Not aggressive
23	F	12	Vocalisation, IE	SA	Not aggressive
24	F	15	Vocalisation, destructive	SA	Not aggressive
25	M	13	Nervousness, destructive	GA	Not aggressive
26	M	36	Aggressive	AGG	Aggressive
27	M	18	Nervousness, vocalisation, destructive	SA	Not aggressive
28	M	24	Fear, vocalisation, destructive	GA	Not aggressive
29	F	84	Aggressive	AGG	Aggressive
30	F	36	Aggressive	AGG	Aggressive
31	M	48	Aggressive	AGG	Aggressive
32	F	42	Aggressive	AGG	Aggressive
33	F	38	Fear, vocalisation	NPh	Not aggressive
34	M	36	Destructive, IE	GA	Not aggressive
35	F	40	Nervousness, fear	GA	Not aggressive
36	F	52	Vocalisation, nervousness	GA	Not aggressive

M, male; F, female; IE, inappropriate elimination; AGG, aggression; SA, separation anxiety; GA, generalised anxiety; OCD, obsessive–compulsive disorder; NPh, noise phobia; Aggressive, anxious dogs with aggression; Not aggressive, anxious dogs without aggression.

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