

Comparison of diazepam with progestin for effectiveness in suppression of urine spraying behavior in cats

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Summary: *The most common treatment for urine spraying and marking in cats has been administration of long-acting progestins. Treatment with diazepam has recently been gaining favor, particularly because of reported adverse effects of progestins. Results of a clinical trial involving 20 cats indicated that diazepam was effective in eliminating or markedly reducing spraying in 11 (55%) of them. However, most cats required continuous treatment, or at least intermittent treatment, when spraying recurred. The physiologic and behavioral dependency of cats on diazepam, which presumably develops over the course of administration, may contribute to the tendency for spraying to recur once diazepam treatment is discontinued. Using data from previously published findings on progestin administration, plus additional cases, it was documented that a significantly ($P < 0.05$) higher percentage of males than females responded favorably. Although the number of cases was not sufficient for a statistical comparison of diazepam vs progestin treatment with regard to male vs female, possible gender difference in the effectiveness of diazepam was not indicated.*

Urine spraying is the most frequent problem behavior in cats for which veterinary consultation and treatment is sought.¹ Spraying can be a normal behavior in sexually intact adult male cats and is usually eliminated by castration.² However, according to one survey,³ approximately 10% of prepubertally castrated males and 5% of prepubertally spayed female cats spray in the home on a regular basis as adults. Castrated males and spayed females may urine mark in places that are not normal toilet areas, using either the spraying posture or the squatting posture; both forms hereafter will be referred to as spraying. Frequent targets are kitchen appliances, walls, draperies, audio speakers, heating registers, specific places on a carpet, the owner's bed, and clothes of a family member.⁴ Events that are commonly mentioned as evoking spraying in gonadectomized cats include:

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adding a new kitten or adult cat to the household, moving to a new house, forcing an outdoor cat to become an indoor cat, or owners taking an extended trip.^{1,4} By understanding the environmental changes that lead to spraying it may be possible to predict whether a cat will eventually make some adjustment to the new situation or continue to spray if the evoking circumstances are likely to continue owing to continuous or repeated stimuli (as in the addition of new cats into the household). Aside from behavioral management, such as restricting the cat to outdoors, and occasional use of appropriate punishment when a cat sprays in 1 or 2 specific locations, the most common treatment to suppress spraying has been oral administration or injection of a long-acting form of a progestin.⁴ One study estimated that progestins were effective in suppressing spraying in about 30% of cats, although male cats tended to respond more frequently than did female cats.⁵ Recently, oral treatment with diazepam for spraying has been gaining favor. Diazepam is a benzodiazepine drug belonging to the antianxiety group of tranquilizers, and has been reported by Marder⁶ to result in elimination or marked reduction of spraying in 74% of cats treated. Most of the cats resumed spraying after cessation of treatment.

One goal of the study reported here was to compare the effectiveness of diazepam with that of progestins. Also, because development of tolerance has been observed for diazepam in animals and human beings,^{7,8} long-term treatment with diazepam was evaluated to determine whether increasingly higher amounts of the drug would be needed over time to control spraying behavior. Because progestins, including the commonly used megestrol acetate, cause reduced glucose tolerance and suppressed adrenocortical function after only 2 weeks of treatment,⁹ an alternative to progestin administration would be desirable. Side effects of progestin administration have been recently reviewed.¹⁰

Materials and Methods

DIAZEPAM TREATMENT

Cats—The study group consisted of 14 cas-

trated male cats (11 from multiple-cat and 3 from single-cat households) and 6 spayed female cats (5 from multiple-cat and 1 from single-cat households) referred for urine spraying or marking. Twelve cats were from the teaching hospital at the University of California, Davis, and 8 were from cooperating small animal hospitals. Of these 20 cats, 11 had been treated with progestins by referring veterinarians, and had not responded. The median age of the cats at time of referral was 3.75 years.

Treatment—Cats were administered diazepam,^a 1 to 2 mg/cat every 12 hours (dose used originally by Marder⁶), for an initial 2-week trial period. If spraying was eliminated or reduced to the point that the client was satisfied (favorable reduction), this dose was continued for a 6- to 8-week treatment period. If spraying did not subside in the initial 2-week trial, the dose was increased by 50% for another 2-week trial. For cats that responded favorably to this increased dose, treatment was continued for 6 to 8 weeks. If a cat still sprayed during the higher dose trial, diazepam administration was decreased gradually over the next 2 weeks, then discontinued. After the treatment period, diazepam treatment was gradually reduced; if spraying did not recur, further treatment was not given. If, however, spraying recurred, diazepam, at the previous effective dose, was resumed for long-term treatment, the nature of which was decided by consultation with the client. The long-term treatment regimen varied somewhat from cat to cat. For example, some clients treated their cats continuously for 5 months or longer; others treated their cat for a few months, discontinued treatment, then initiated treatment again if spraying recurred. Data on the response of the cats to diazepam were gathered from frequent telephone consultations with the owners, and the degree of urine spraying, if any, was assessed. All clients were asked about any side effects of diazepam treatment, including incoordination (ataxia), excess sleeping or lethargy, and changes in appetite.

PROGESTIN TREATMENT

To have a data base with which to compare the relative effectiveness of diazepam with that of progestins on spraying in male vs female cats, some data were used from a previously published study of progestin treatment,⁵ supplemented by additional cats referred for urine spraying or marking and treated with progestins since the published study. Progestin treatment consisted of injection of medroxyprogesterone acetate (MPA; 100 mg/cat for males, 50 mg/cat for females, SC) or oral treatment with megestrol acetate (MA; 5 mg/cat/d for 7 to 10 days followed by gradually decreasing the dose over the subsequent 6 months). Because the previous study did not indicate difference in effectiveness of MPA vs MA, data from both types of proges-

tin treatments were pooled, yielding 60 cats (35 males and 25 females). All cats had been gonadectomized at a median age of 7 to 8 months. Treatment was judged to be successful if problem urine spraying or marking ceased or was markedly reduced for at least 1 month.

Of course, the treatment regimens of diazepam and progestin varied, and to some degree, this reflected the duration of action of the drugs. Blood concentration half-life of progestins has been estimated at 8 days for MA and 45 days for MPA.⁵ In some instances, long-term treatment with progestins has been found necessary to control spraying, and it is not unusual to see cats treated weekly or biweekly with MA for a year or longer (data not shown). Comparison of progestin with diazepam treatment was based only on the question of whether treatment was favorable during the initial treatment period.

Results

Of the 20 cats treated with diazepam, 11 responded favorably during the trial and treatment periods. Nine cats underwent complete cessation of spraying, and 2 cats underwent marked decrease of spraying to a level acceptable to the owner. Data from cats that completely stopped spraying, or that underwent acceptable reduction, were pooled together for data presentation and were referred to as having favorable response. Of the 11 cats previously treated with a progestin, 5 responded favorably to diazepam treatment. Only 1 cat did not resume spraying when diazepam administration was discontinued after the 6- to 8-week treatment period. The other 10 cats that resumed spraying after the treatment period were long-term treated continuously (long-term; n = 6) or treated intermittently when spraying resumed (n = 4). At the time this study was completed, long-term treatment periods had ranged from 6 months to 4 years. Repeat treatment after an interval without treatment did not require an increased dose to suppress spraying. In one cat when diazepam was discontinued after continuous treatment for 11 months, spraying had not recurred. The 5 other cats on continuous long-term treatment resumed spraying after attempts were made to gradually discontinue treatment. Three of these cats have been treated continuously for 3 to 4 years with no increase in the dosage and with no return of the spraying. Communication with the owners of the 2 other cats on continuous long-term treatment was lost after 6 months.

Data were gathered regarding gender and household status of cats during the treatment period (Table 1). There were too few cats from single-cat households to draw any conclusions about the influence of household status on diazepam effectiveness. Of the cats from multiple-cat households, 7 of the 11 males (64%) and 3 of the 5 females (60%) responded favorably, suggesting no apparent gender difference (Fig 1).

^aValium, Roche Nutley, NJ.

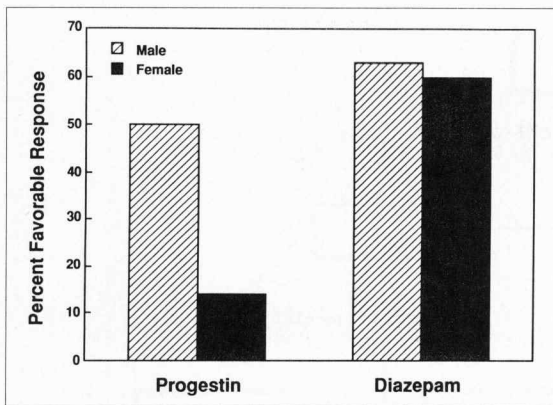


Figure 1—Percentage of male and female cats from multiple-cat households responding favorably to progesterin or diazepam. The difference in gender responsiveness was significant for progesterin ($P < 0.05$).

Table 1—Number of cats treated for urine spraying or marking and responding positively (Pos) or negatively (Neg) to diazepam or progesterin treatment

Treatment	Gender	Household Type			
		Multiple-cat		Single-cat	
		Pos	Neg	Pos	Neg
Diazepam	Male	7	4	1	2
	Female	3	2	0	1
Progesterin	Male	14	14	6	1
	Female	2	12	3	8

With regard to side effects of diazepam treatment, 8 owners reported that their cats were noticeably atactic at the onset of treatment. This side effect generally disappeared within 5 days except in 3 instances, where ataxia continued and was of sufficient concern to cause the owners to discontinue use of the drug (no suppression of spraying). Increased sleepiness was noticed in 10 cats and, in 3, became a serious concern. Increased appetite (3 cats), weight gain (2 cats), reduced aggression toward another cat (1 cat), and a calmer or more affectionate temperament toward people (3 cats) were changes reported.

Of the cats treated with progesterin, 25 of 60 (42%) responded favorably (Table 1). In males and females, higher percentage of cats from single-cat households responded favorably than those from multiple-cat households, but these differences did not reach statistical significance. A higher percentage of males than females responded favorably to progesterin treatment (Fig 1), and this gender difference reached significance whether the analysis included cats from single- and multiple-cat households or just multiple-cat households ($P < 0.05$; Fisher's exact test). With regard to responses of male vs female cats, a statistically significant difference between progesterin and diazepam treatment could not be observed because diazepam data were insufficient.

Discussion

Diazepam was effective in stopping spraying in 9 cats and markedly reducing spraying in 2 of 20 cats during the 2-week trials and subsequent 6- to 8-week treatment periods. Cats that were reported to no longer spray may still have sprayed in places undetected by the owners. Thus, it seemed logical for data analysis to group all favorably responding cats together. Of the 11 cats (55%) that responded favorably to diazepam treatment, only 1 did not resume spraying when diazepam was gradually reduced after the initial treatment period of 6 to 8 weeks. The other 10 resumed spraying when diazepam was discontinued after the treatment period. Eight of these cats resumed spraying almost immediately after reduction of the dosage and 6 were successfully treated continuously for 6 months to 4 years. One cat did not resume spraying after discontinuation of treatment after 1 year. The remaining 2 cats only sprayed intermittently after discontinuation of the 6- to 8-week treatment and were treated intermittently when spraying recurred. Increase in dose was not found necessary for long-term treatment. The study by Marder⁶ involved treating cats with diazepam for only 1 month (followed by 1 month of gradual reduction). That author found that 43% of cats completely stopped spraying and another 32% markedly reduced spraying by at least 75%. That author also found that after cessation of treatment, 75% of cats that had responded favorably resumed spraying later. Thus, on the basis of results of this study and those reported by Marder,⁶ it appears that successful treatment of urine spraying by diazepam will usually require commitment to twice daily treatment for a year or longer. On the basis of findings of our study, a specific treatment regimen is recommended (Fig 2). The flow chart takes into account the responsiveness of a cat to diazepam and the wishes of the client as to whether to maintain treatment continuously or intermittently. Perhaps, as other psychoactive drugs are tested for treatment of urine spraying, this flow chart could serve as a useful model.

Findings of the study indicate that the dose of diazepam required to suppress spraying does not have to be increased during long-term treatment. This is interesting inasmuch as tolerance to the sedative effects of diazepam is reported in laboratory animals.⁷ Diazepam treatment can induce physiologic and behavioral dependency, including tremors, twitches, hyperactivity, and increased anxiety for 2 weeks after withdrawal.⁷ Cats, in fact, are used as models to study the dependence-inducing effects of diazepam.⁸ Recurrence of spraying in cats, when treatment is discontinued after several months or a year of treatment, could reflect an emotional disturbance related to diazepam dependence, and thus, the requirement for long-term treatment could be self-reinforcing. Because dependency has been shown for benzodiazepines in

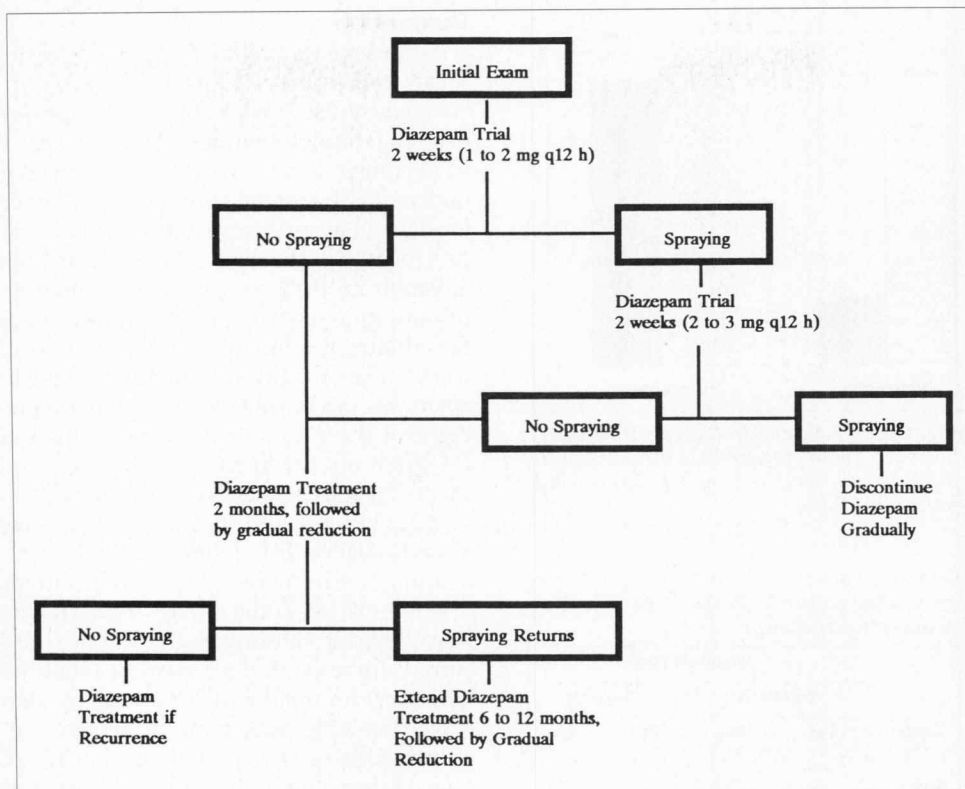


Figure 2—Flow chart for suggested treatment regimen of urine spraying (marking) by use of diazepam. Because of physiologic and behavioral dependency that is acquired to benzodiazepine drugs, discontinuance of treatment should always be gradual.

general, use of other benzodiazepines is unlikely to eliminate the dependency problem.⁷ Clearly, when a cat has been administered diazepam for a long period, withdrawal of the drug should be gradual. Some drugs are currently under study for use in ameliorating the physical effects of benzodiazepine withdrawal,⁷ and these may prove useful in affected cats.

The trials with diazepam did not point to no difference between treatment effectiveness in male vs female cats. Until further information is available, it would appear as though one can expect better response from female cats with diazepam (50% in this study) than with progestin (20% in this study), whereas the response of males may be about the same (about 50% to both drugs). Forty-five percent of cats that did not respond previously to progestin treatment responded favorably to diazepam. In Marder's study⁶ diazepam suppressed spraying in all cats that had not responded to progestins.

The indications that diazepam and progestin affect spraying behavior differentially point to the possibility that there may be 2 separate underlying neural substrates for spraying and that the 2 drug types act differentially on these substrates. This viewpoint is consistent with studies indicating that progestins are bound by cytosolic androgen receptors with direct inhibiting effects on 5 α -steroid reductase¹¹ in neurons located within the hypothal-

amus and limbic system,¹² but diazepam is bound by specific benzodiazepine receptor sites throughout the neural axis and induces depression of neural activity through enhancement of γ -aminobutyric acid, an inhibitory neural transmitter.¹³

Further evidence for 2 separate neural substrates comes from the effects of various neurologic lesions induced clinically in cats not responding to progestins. Bilateral medial preoptic-anterior hypothalamic lesions, which typically eliminate or markedly reduce male sexual behavior,¹⁴ eliminated spraying in male cats but not in female cats.¹⁵ Olfactory tractotomy, on the other hand, eliminated spraying in female cats more frequently than in male cats.¹⁶ Olfactory tractotomy may affect behavior by interfering with the animal's sense of smell or may induce neurologic changes in the limbic system in ways unrelated to the loss of olfaction.^{17,18}

According to such a dual-system hypothesis, spraying in some cats may be mediated by the same substrate that mediates male sexual behavior and involves the medial preoptic-hypothalamic axis. This would be the system that is predominantly suppressed by progestin administration and by induction of medial preoptic-anterior hypothalamic lesions. Spraying mediated by this system would be mostly expressed in males but could be expressed in females because both genders have the neuronal systems for homotypical as well as heterotypical

sexual behavior.^{14,19} With this type of spraying, males would thereby respond more frequently than females to progestin treatment. Spraying mediated by the second system would reflect the expression of anxiety and involve structures that have benzodiazepine or other anti-anxiety-drug receptors. Anxiety-mediated spraying would, theoretically, be observed about equally in males and females, and presumably, both genders would respond about the same to diazepam treatment, as data from this study suggest. It is conceivable that spraying in a particular cat may reflect the activation and/or interaction of the 2 mediating systems, and in such instances, either drug type may have some influence on the behavior.

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