Retrospective evaluation of the effects of diazepam in dogs with anxiety-related behavior problems

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Objective—To characterize the effects of diazepam in dogs with behavior problems and to determine whether adverse effects were of sufficient concern to owners to prompt drug discontinuation.

Design—Cross-sectional study.

Sample Population—37 dogs and their owners.

Procedures—Dogs for which diazepam had been prescribed by the behavior service of a veterinary teaching hospital from July 2005 through June 2007 were identified. Owners were interviewed via telephone to obtain data on dose and frequency of administration of diazepam, effectiveness, adverse effects, and, when applicable, reasons for discontinuing the drug.

Results—Diazepam was described as very (24% [9/37]) or somewhat (43% [16/37]) effective by most owners. At the time of the interview, 18 (49%) owners reported that they were still administering diazepam to their dogs. For the remainder, reasons for discontinuation included adverse effects (58% [11/19]) and lack of efficacy (53% [10/19]). Reported adverse effects included sedation, increased appetite, ataxia, agitation, increased activity, and aggression. Owners administering diazepam to ameliorate fear of thunderstorms (24% [9/37]) were more likely to view diazepam as effective than were owners of dogs that received it for separation anxiety (54% [20/37]). Owners of dogs that received 0.8 mg of diazepam/kg (0.36 mg/lb) were more likely to report increased activity as an adverse effect than were owners of dogs that received < 0.8 mg/kg.

Conclusions and Clinical Relevance—Adverse effects of diazepam in dogs were commonly reported and often led to drug discontinuation. Owner education and follow-up is recommended to avoid treatment failure when prescribing diazepam for anxiety-related behavior problems in dogs. (J Am Vet Med Assoc 2008;233:1420–1424)

Anxiety in animals is an emotional response to a stimulus that predicts a potentially harmful situation. The response is manifested as a variety of stress-related behaviors such as panting, pacing, vocalization, and elimination.1 Anxiety-related behavior problems in dogs can be severe, leading to self-injury, property destruction, and in some situations, owner-elected euthanasia.2 Veterinarians can assist owners in the management of anxiety-related behaviors with an appropriate combination of medical intervention, environmental changes, and behavior modification tools. Treatment of anxiety-related behavior problems often includes benzodiazepines such as diazepam.2,3

Diazepam is used for its anxiolytic and sedative-hypnotic properties in human patients with panic and anxiety disorders.1,5,6 Adverse effects reported by those taking diazepam or other benzodiazepines include drowsiness, ataxia, paradoxic excitement, constipation, and nausea.1 In veterinary behavioral medicine, diazepam is used in the management of separation anxiety, fear of thunderstorms or loud noises, and other fear or anxiety-related problems in dogs.2,3 Owner-reported adverse effects of diazepam administration in dogs include ataxia, undesirable or excessive sedation, increased appetite, paradoxic excitement, or agitation.1,7

Some effects of benzodiazepines can be disturbing to owners and may interfere with the behavior modification process. For example, a dog with paradoxic excitement is unlikely to remain calm during a thunderstorm and perhaps even less likely to be successfully counterconditioned8 to the frightening stimulus. Increased appetite may result in intense food-seeking behaviors, leading to weight gain, destructiveness, and ingestion of nonfood items. Owners of dogs that exhibit such behaviors may be reluctant to continue treatment with diazepam, even when there is otherwise some clinical benefit from reduction of fear and anxiety. Although adverse effects of benzodiazepines in dogs have been reported, the frequency with which they occur has not been systematically evaluated.

The objectives of the study reported here were to characterize the effects of diazepam in dogs with behavioral problems as reported by dog owners and to determine whether the described effects were sufficiently disturbing to owners to prompt discontinuation of the medication.

Materials and Methods

Animals—All medical files of dogs evaluated by the behavior service of the Matthew J. Ryan Veterinary Hos-
hital of the University of Pennsylvania between July 1, 2005, and June 30, 2007, were retrospectively examined. Dogs were eligible for inclusion in the study when diazepam had been prescribed for them by the behavior service at any point during the 2-year period. Owner information (name and phone number) and dog data (indication for diazepam use, prescription information, signalment, and body weight) were also collected from the records. Although the primary problem for which dogs had been evaluated varied, anxiety was identified in all dogs for which diazepam was prescribed. To avoid causing emotional distress of owners, dogs that were identified in the records as euthanatized were excluded.

Owners of dogs that met the inclusion criterion were contacted by a research assistant by telephone to obtain consent for a 10-minute survey. When the telephone was not answered but messages could be recorded, a message was left regarding the study and providing a return telephone number. Ten contact attempts were made before owners were considered to be nonresponders. Owners who chose to participate were interviewed regarding diazepam administration and its effect on their dog. Potential participants were excluded when they had never administered the prescribed drug or when they could not recall how diazepam affected their dog.

Telephone survey—The survey instrument included questions regarding dose and frequency of administration of diazepam, whether the owner continued to administer the drug after initial administration, the owner’s perception of the effectiveness of diazepam, specific adverse effects detected, and, when applicable, reasons for discontinuing the drug. Owners were asked to rate the effectiveness of diazepam for its prescribed indication as very effective, moderately effective, slightly effective, or not effective. Because the terms moderately and slightly are subjectively similar, responses of moderately and slightly effective were collapsed into 1 category (somewhat effective) for statistical analysis. Potential adverse effects listed in the survey were sedation, increased appetite, ataxia, excitation, agitation, vomiting, diarrhea, constipation, new aggression, and increased existing aggression. Each adverse effect was first defined by the interviewer. Although sedation is often a desired effect when diazepam is prescribed, it was considered an adverse effect so that excessive sedation could be characterized.

Because there is a wide anxiolytic dose range and dose may have been adjusted after the initial consultation, the actual administered dose of diazepam for each dog was confirmed by the research assistant at the start of the interview. Information on high and low dosages was collected to examine the relationship between dose and frequency of adverse effects of diazepam. When >1 dosage had been administered, owners were asked about adverse effects associated with the high and low dosages of diazepam they had given to their dogs. When no dosage adjustment was made and only 1 dosage was administered, owner responses were treated as if they related to the low dosage (ie, no data were recorded for adverse effects associated with high a dosage). When owners reported a listed adverse effect, they were asked to rate the degree to which it bothered them by choosing from 3 options: very much, somewhat, or not at all. For statistical analysis, the responses very much and somewhat were collapsed into 1 category (bothered). The survey was reviewed and granted exemption status by the University of Pennsylvania Institutional Review Board in regard to the enrollment of human participants.

Statistical analysis—Data are presented as frequencies and percentages for categoric data and means with ranges for continuous data (ie, age, body weight, and drug dosage). To detect differences in effectiveness (effective vs not effective) by primary complaint, a Fisher exact test was used. To determine whether dosage (low vs high dosage) was related to any specific adverse effect, a Fisher exact test was again used. A value of P < 0.05 was considered significant. All analyses were performed with statistical software.

Results
Fifty-one owners of dogs for which diazepam was prescribed were eligible for the study. Telephone interviews were successfully completed with 37 (73%) of those owners. Seven owners (14%) could not be contacted after 10 attempts, 3 (6%) declined participation in the survey, and 4 (8%) reported that they never administered diazepam to their dogs.

Of the dogs in the study, 17 (46%) were ovariohysterectomized females, 19 (51%) were castrated males, and 1 (3%) was a sexually intact male. Twenty were mixed-breed dogs, and 16 were purebred dogs of various breeds. Mean age was 6.6 years (range, 3 to 14 years). Mean body weight of the dogs as recorded in the medical record was 23 kg (50.6 lb; range, 3 to 44 kg [6.6 to 96.8 lb]).

The mean low dosage of diazepam prescribed was 0.7 mg/kg (0.32 mg/lb; range, 0.2 to 1.2 mg/kg [0.09 to 0.55 mg/lb]), and the mean low dosage reportedly administered was 0.5 mg/kg (0.23 mg/lb; range, 0.15 to 1.2 mg/kg [0.07 to 0.55 mg/lb]). The mean high dosage prescribed was 1.4 mg/kg (0.64 mg/lb; range, 0.7 to 2.0 mg/kg [0.32 to 0.91 mg/lb]), whereas the mean high dosage administered was 1.0 mg/kg (0.45 mg/lb; range, 0.3 to 2.3 mg/kg [0.14 to 1.05 mg/lb]). When data regarding low and high dosages were averaged, the mean administered low and high dosages were lower than the mean prescribed low and high doses.

Behavioral problems for which dogs were initially evaluated included separation anxiety (n = 20 [54%]), stranger-directed aggression (11 [30%]), owner-directed aggression (7 [19%]), aggression toward dogs (7 [19%]), nonspecific (owner-reported) anxiety (6 [16%]), fear of thunderstorms (6 [16%]), fear of specific noises (3 [8%]), confinement anxiety (2 [5%]), fear at the veterinary office (2 [5%]), and 1 (3%) indication each of generalized anxiety, fear of grooming, and anxiety during boarding or car travel (Figure 2). Diazepam
was prescribed to treat 5 dogs that had > 1 behavioral problem.

Fifteen (41%) owners administered diazepam to their dog 1 to 3 times only. An additional 13 (41%) reported that they gave their dog diazepam only as needed, whereas 7 (19%) owners gave it to their dog daily. In most situations, another anxiolytic agent, specifically fluoxetine (n = 19 [51%]), clomipramine (9 [24%]), or sertraline (2 [5%]), was administered on a daily basis, concurrently with the diazepam. Seven dogs (19%) were not given any medication other than diazepam.

Diazepam was described as very effective by 9 (24%) owners, somewhat effective by 16 (43%) owners, and not effective by 12 (32%) owners. Owners of dogs that were treated with diazepam primarily because of fear of thunderstorms (n = 9 [24%]) were significantly (P = 0.01) more likely to describe diazepam as somewhat effective or very effective than owners of dogs for which it was prescribed primarily because of separation anxiety (20 [54%]; 100% vs 50%, respectively).

At the time of the interview, 18 (49%) owners reported that they were still administering diazepam to their dog, 10 (27%) were not given any medication other than diazepam, whereas 7 (19%) owners gave it to their dog daily. An additional 15 (41%) reported that the drug was no longer needed (to manage anxiety from confinement). Reported adverse effects leading to discontinuation were agitation (n = 6 [32%]), increased activity (5 [26%]), ataxia (5 [26%]), increased appetite (2 [11%]), diarrhea (1 [5%]), and vomiting (1 [5%]).

Owners who administered diazepam on an as-needed basis (n = 15) were significantly (P < 0.001) more likely to be still administering this medication (13 [87%]) at the time of the survey than were owners who administered it daily (57% [4/7]) or seldom (only 1 to 3 times in total; 7% [1/14]).

Owners reported sedation, ataxia, increased activity, agitation, and increased appetite at both dosages (high and low), although some owners reported specific effects at 1 dosage only (Table 1). Of the 22 owners who reported sedation in their dogs, 8 (36%) were concerned about it, whereas 13 (59%) were not. Half of the 16 owners who reported increased appetite were bothered by this effect. Ataxia was reported by 23 (62%) owners, of whom 17 (74%) were bothered by it. One owner was unconcerned about the mild sedative and ataxic effects that were evident at the low dose but was bothered by the degree of sedation and ataxia resulting from the high dose. Increased activity was reported for 10 dogs (27%), and 7 owners (70%) were disturbed by it. Twelve owners (32%) reported that their dogs became agitated, and 10 (83%) were bothered by that effect.

One owner each described diarrhea or vomiting; both were concerned about it. Constipation was not reported. Two (5%) owners reported new aggression, and 3 (8%) reported an increase in existing aggression in their dogs. All owners who reported aggression were bothered by this apparent effect of diazepam.

Owners who administered dosages of ≥0.8 mg/kg (0.36 mg/lb) were significantly (P = 0.03) more likely to describe increased activity as an adverse effect than were those.

### Table 1—Frequencies of adverse effects of low (0.5 mg/kg [0.23 mg/lb]; range, 0.15 to 1.2 mg/kg [0.07 to 0.56 mg/lb]) and high (1.0 mg/kg [0.45 mg/lb]; range, 0.3 to 2.3 mg/kg [0.14 to 1.05 mg/lb]) dosages of diazepam in 37 dogs with anxiety-related behavior problems, as reported by owners.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>No. (% of dogs at low dosage alone</th>
<th>No. (% of dogs at high dosage alone</th>
<th>No. (% of dogs at both dosages</th>
<th>Total No. (%) of dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>9 (24)</td>
<td>6 (16)</td>
<td>7 (19)</td>
<td>22 (59)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>9 (24)</td>
<td>9 (24)</td>
<td>5 (14)</td>
<td>23 (62)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>5 (14)</td>
<td>5 (14)</td>
<td>6 (16)</td>
<td>16 (43)</td>
</tr>
<tr>
<td>Agitation</td>
<td>6 (16)</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Increased activity</td>
<td>4 (11)</td>
<td>4 (11)</td>
<td>2 (5)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Increased aggression</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>0</td>
<td>3 (8)</td>
</tr>
<tr>
<td>New aggression</td>
<td>2 (5)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
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</table>
who administered < 0.8 mg/kg. No other dose-related differences were detected.

Discussion

In the study reported here, diazepam was prescribed for treatment of dogs with a variety of anxiety-related behavior problems. The most common problems were separation anxiety and fear of thunderstorms. Although the behavior problems for which dogs were treated prompted the initial behavioral evaluation in some situations, in other situations, this was not true. For example, a dog may have been initially evaluated for aggression toward unfamiliar dogs but it may have also had a fear of thunderstorms or it may have needed sedation for grooming.

Whereas treatment of dogs with diazepam for anxiety problems was considered at least somewhat effective by most dog owners in the study reported here, more owners of dogs that feared thunderstorms believed that the drug was effective than did owners of dogs with separation anxiety. The difference might have been related to the frequency of distressing events. Thunderstorms typically occur less frequently than do owner departures, and dogs with separation anxiety are likely to be exposed to owner departures at least several times per week. In addition, owners may be at home with their dog during storms and thus, unlike owners of dogs with separation anxiety, may have the opportunity to distract and reassure their dogs. We did not have objective measures of severity of the behavioral indications for diazepam use. Perhaps dogs that were evaluated for separation anxiety displayed more severe signs of distress or self-injury than did dogs with fear of thunderstorms. More information would be needed to draw conclusions about efficacy of diazepam for treatment of dogs with separation anxiety or other disorders.

Only 1 person reported resolution of the behavior problem as a reason for discontinuation of the diazepam. There are several possible reasons for the lack of others reporting the same reason. First, the anxiety-related behavior problems in the dogs of the present study may have been severe enough to require long-term therapy. Second, owners of dogs that responded to treatment may have been reluctant to discontinue a medication that was helping their dog. It would make sense that successful treatment might be continued, whereas unsuccessful treatment would not.

In contrast, more than half the owners in our study were no longer administering diazepam despite their impression that the drug was effective. Many reported adverse effects as a reason for discontinuation. Ataxia was the most frequently reported adverse effect and was considered the most bothersome to owners. Clients of the behavior clinic at our hospital are routinely counseled regarding the risk of adverse effects. However, owners may have been concerned for the safety of their dogs around stairs or furniture, particularly when they were using the drug at times the dog was alone and unsupervised.

Agitation and increased activity were bothersome to most owners who reported these adverse effects of diazepam. Like ataxia, these effects prompted discontinuation of treatment by owners in many situations. Such effects are similar to the paradoxic reactions described in the human medical literature. Paradoxical agitation secondary to benzodiazepine administration can occur in animals as well as humans (particularly children or adolescents). Because agitated behavior tends to be similar to the distressed or anxious behaviors for which treatment is sought, it was not surprising that owners discontinued administration of diazepam to their dog.

Increased appetite was a commonly reported adverse effect of diazepam administration. This finding is consistent with findings in other animal species. Owners were evenly distributed between those who were concerned about the increased appetite and those who were not. Unlike ataxia and agitation, increased appetite was not a common reason for discontinuation of the drug. Increased appetite may be a desirable effect in some dogs with fear or anxiety. For example, a common recommendation for management of separation anxiety is the use of food-stuffed toys and bones as a distraction and a means of conditioning a positive association with owner departures. However, dogs with separation anxiety are typically uninterested in food when owners are absent; therefore, increased appetite may be desired. Owners may also perceive improvement if their dog were to eat during events that the dog previously perceived as stressful. However, increased appetite can also lead to destructive food-seeking behaviors and ingestion of nonfood items.

The potential for diazepam and other benzodiazepines to disinhibit or increase aggressive tendencies in dogs and other species has been described. Aggression is an unacceptable effect because of its potential for increased aggression is reported for many psychotropic drugs. Owners of dogs evaluated by our behavior service are counseled with regard to the potential for aggression with benzodiazepine use. Because fear underlies many aggression problems, anxious dogs may be predisposed to irritable and aggressive behavior, regardless of whether diazepam is administered. In our study, it was not surprising that owners who witnessed aggression in their dog discontinued treatment with diazepam because, in most situations, owners who reported increased or new aggression to staff at the behavior clinic were also instructed to discontinue diazepam.

Sedation of dogs treated with diazepam was reported by most owners in our study. Although sedation is typically a desired effect of diazepam, more than a third of owners who reported sedation also reported being bothered by it. Excessive sedation may be undesirable; however, regular use of benzodiazepines should lead to a decrease in degree of sedation with maintenance of anxiolyis. Although sedation is regarded unfavorably by some owners, it effectively decreases the manifestations of fear and anxiety and may help prevent exacerbation of fear with ongoing exposure to fear-inducing stimuli. It is

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important, however, for veterinarians to alert owners to the likelihood and benefits of temporary sedation in the management of canine fears and anxieties.

Owners in our study administered a wide range of dosages to their dogs, making comparisons of dose and effect difficult. The only adverse effect of diazepam that appeared to be dose dependent was increased activity. It has been suggested that increasing the dosage of benzodiazepine when paradoxical excitement is encountered may help to decrease the degree of excitement. In contrast, the results of our study indicated that excitement and increased activity were more common in dogs treated with high dosages of diazepam. However, because of our small sample size, we could not conclude that a specific dose of diazepam was more effective or less likely than another to cause adverse effects.

The dosing frequency of diazepam for the indications for which it was prescribed varied among the dogs in the study reported here. Most owners did not administer diazepam every day. Because most indications for diazepam use in our study involved discrete events that typically did not occur on a daily basis, owners were more likely to have used this medication on an as-needed basis or to have used it infrequently. Administration of diazepam as needed allows for fast-acting, short-term anxiolysis while avoiding the potential development of tolerance—particularly to sedation—associated with daily use. Although tolerance and the resulting need to increase the dose with time are avoided with intermittent administration, acclimation to any adverse effects may also be forfeited with this dosing pattern. Several factors may explain why owners administered a lower dosage, on average, than was prescribed for their dog. First, some owners may have anticipated and attempted to avoid the adverse effects described to them at the initial behavior consultation. Although increased activity was the only effect that appeared to be dose dependent, some owners may have (perhaps incorrectly) assumed that adverse effects would become magnified at higher dosages. Second, in many situations, the small tablet formulation of diazepam required administration of several tablets at once. For example, at a dosage of 0.5 to 2.0 mg/kg, a 20-kg (44-lb) dog could require up to 40 mg of diazepam to achieve a therapeutic effect. At the 10-mg formulation, this would require administration of 4 tablets at once, which some owners may have perceived as inconvenient. Finally, the usual dosage of diazepam in the treatment of humans with anxiety is lower than the dosage for dogs with the same problem, which may have contributed to a reluctance of owners to administer the recommended dosage.

Our study was limited in several respects. A possible confounding factor was the coadministration of another anxiolytic besides diazepam on a daily basis, which was the situation in most dogs. The inclusion criterion needed to be broad to achieve a reasonable sample size; exclusion of dogs that received other anxiolytics would have reduced our sample size to 7. We relied on the short duration of action of diazepam in dogs and anticipated that its adverse effects would be evident for a few hours only. Thus, we believed it would be possible for owners to distinguish between the more persistent therapeutic or adverse effects of the other drug and the temporary effects of diazepam.

Another confounding factor was that behavior problems and their severity differed among dogs, as did dosages of diazepam. In addition, the effects of (or compliance regarding) environmental and behavior modification, other than diazepam use, were not evaluated. More compliant owners who were able or willing to apply behavioral or environmental modification techniques and administer diazepam may have been more likely to believe that diazepam was effective; however, this possibility was not assessed in our study.

The finding that increased agitation occurred with high dosages of diazepam suggested that veterinarians should prescribe low dosages of diazepam, at least initially and before adjusting the dosage, or choose a different anxiolytic such as clorazepate or oxazepam if this adverse effect is observed. Ataxia, agitation, and increased activity led to discontinuation by most owners who observed these effects in their dogs. These results highlight the importance of owner education regarding potential adverse effects and close follow-up by veterinarians to avoid treatment failure when diazepam is prescribed to treat dogs with anxiety-related behavior problems.

a. Copies of the telephone survey are available from the corresponding author on request.


References