Benzodiazepines: Pros and Cons for Fear and Anxiety

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Of the thousands of benzodiazepine molecules that have been synthesized in the laboratory, only a few are commercially available. At this time, none are approved by the US Food and Drug Administration for the treatment of behavior problems in domestic animals. However, several benzodiazepines marketed for use in humans are commonly used in animals, especially for the treatment of anxiety disorders, fears, and phobias (Table 1). Benzodiazepines facilitate $\gamma$-aminobutyric acid (GABA) activity in the central nervous system by binding to GABA$\text{A}$ receptors and enhancing the receptors’ opening frequency. GABA is the most common inhibitory transmitter in the brain. The behavioral effects of benzodiazepines are primarily a result of action in the hypothalamus and limbic system, where they affect vigilance, anxiety, muscle tension, epileptogenic activity, and memory.$^1$

**INDICATIONS**

One of the major advantages of benzodiazepines is their rapid onset of action. Relief from anxiety can be attained in 30 to 60 minutes with the appropriate drug and dose. This is important because it is not uncommon for owners to notify their veterinarian of a pet’s unacceptable fear-induced behavior only after the problem has become so severe that they are ready to euthanize or give up the pet if there is no immediate solution. Although true, long-term resolution of fear-induced behavior problems requires weeks to months of treatment, often with the use of other medications and treatment modalities, including desensitization and counterconditioning, benzodiazepines may provide an essential window of calmer behavior so that the family is more willing to attempt the treatment that will provide a longer-term solution. For example, in separation anxiety, treatment with serotonin reuptake inhibitors (SRIs) such as clomipramine (Clomicalm, Novartis) and fluoxetine (Reconcile, Eli Lilly) has been shown to be more effective than behavior modification alone. However, the onset of action of these drugs takes a minimum of several days, and weeks may be required for the drugs to achieve full efficacy. If the family is unwilling to wait the necessary time for SRIs to take effect, supplementation of the pet’s regimen with a benzodiazepine can often keep the pet calm through the early stages of treatment.$^2$

Benzodiazepines are commonly used to treat anxieties, fears, and phobias without aggression. Their use in the treatment of fear with aggression is controversial. Although they may be beneficial in the treatment of fear-induced aggression by decreasing the underlying motivation for the aggression, they may also cause a loss of learned inhibitions. If this occurs, the pet may be more likely to exhibit overt aggressive behavior because the alleviation of fear is inadequate and the pet’s behavior is less controlled. As a general rule, benzodiazepines should not be used as first-line treatment in cases of fear aggression. However, they may be tried in animals that do not show adequate

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improvement with other treatment modalities. In these cases, the owners should be instructed to exhibit extra caution when administering the first few doses and observe whether the pet becomes more aggressive or shows substantial improvement as its fear abates.

**TREATMENT CONSIDERATIONS**

When starting a pet on a benzodiazepine, it is best to begin at a low to medium dose. Ideally, the owner should administer the first dose when he or she can stay home with the pet and the situation that causes fear is not occurring so the pet’s response to the medication at that dose can be observed. In most cases, no change in behavior occurs or the pet shows mild sedation. The dose can then be tested under the conditions in which the pet exhibits fear (e.g., the owner leaving the house, during thunderstorms). Occasionally, significant adverse effects, such as significant sedation or paradoxical excitation, are observed with the initial test. If significant sedation occurs, the dose should be decreased. If liver and kidney function has not been recently evaluated, these tests should also be conducted because the pet may not be metabolizing and excreting the medication at a normal rate. Pets that exhibit a paradoxical excitation response may respond well to higher doses, or a different medication may be required.

When the medication is tested under the fear-inducing circumstances, the dose and frequency should be adjusted until the desired response is obtained. If undesirable effects occur before the fear is adequately controlled, it may be necessary to change medications. While the various benzodiazepines are similar, they are not identical, and a pet that exhibits excessive sedation and poor calming with one drug may be relaxed but alert with a different one.

Regardless of the benzodiazepine used, it should only be administered on an “as needed” basis. Thus, for pets with separation anxiety, benzodiazepines should not be given on days when the owners will be home. For pets with storm phobia, benzodiazepines should not be given during clear and pleasant weather. This regimen contrasts with that for SRIs, which must be given daily, regardless of the environment.

The rapid onset of action of benzodiazepines is mirrored by their short period of clinical efficacy, which ranges from 2 to 12 hours. Generally, shorter-acting benzodiazepines are less expensive than longer-acting benzodiazepines, a fact that is relevant to veterinary medicine because clients are usually paying out of pocket for their pet’s medication. In some cases, prescribing two different benzodiazepines to be used in different circumstances can be a cost-effective approach to treatment. For example, if a client has a dog with separation anxiety that responds well to diazepam (3 to 4 hours of clinical efficacy) and clorazepate (6 to 8 hours of clinical efficacy), both drugs may be prescribed for use depending on how long the pet has to be left alone. Clorazepate is substantially more expensive than diazepam. If the client goes out for a short time or can return home to medicate the dog, the less expensive diazepam can be used. However, if the client will be gone for a longer period of time, clorazepate can be administered.

**ADVERSE EFFECTS**

Sedation is the most common adverse effect of benzodiazepines. Other adverse effects include ataxia, muscle relaxation, increased appetite, anxiety,
Table 1. Benzodiazepines Commonly Used in Dogs and Cats

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name (Human)</th>
<th>Canine Dosagea</th>
<th>Feline Dosagea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Xanax</td>
<td>0.02–0.1 mg/kg q4h</td>
<td>0.0125–0.25 mg/kg q8h</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Librium</td>
<td>2.0–6.5 mg/kg q8h</td>
<td>0.2–1.0 mg/kg q12h</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Klonopin</td>
<td>0.1–0.5 mg/kg q8h</td>
<td>0.015–0.2 mg/kg q8h</td>
</tr>
<tr>
<td>Clorazepate dipotassium</td>
<td>Tranxene</td>
<td>0.5–2.0 mg/kg q4h</td>
<td>0.5–2.0 mg/kg q12h</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Valium</td>
<td>0.5–2.0 mg/kg q4h</td>
<td>0.1–1.0 mg/kg q4h</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>0.1–0.5 mg/kg q12h</td>
<td>0.1–0.4 mg/kg q12h</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Ativan</td>
<td>0.02–0.5 mg/kg q8h</td>
<td>0.03–0.08 mg/kg q12h</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Serax</td>
<td>0.04–0.5 mg/kg q6h</td>
<td>0.2–1.0 mg/kg q12h</td>
</tr>
</tbody>
</table>

*a* The dose frequency given is the maximum frequency that should be used. The lowest dose and frequency that alleviate the fear should be used. All the drugs listed are administered orally.

hallucinations, muscle spasticity, insomnia, and idiopathic hepatic necrosis. The last effect has occurred in several cats specifically as a consequence of the administration of diazepam. While there are several theories as to why a small number of cats exhibit this idiopathic response, the underlying mechanism of liver failure in cats given diazepam is not understood. Therefore, the other benzodiazepines are probably better choices for cats.

**Addiction**

The advantage of rapid onset of action is also a potential problem. Benzodiazepines are psychologically and physically addictive in humans and are listed by the Drug Enforcement Administration as schedule IV drugs. As a result, some pet owners may attempt to use their pets to get prescriptions for benzodiazepines from their veterinarians. When long-term benzodiazepine therapy is prescribed for a pet, the number and frequency of refills, as well as the pet’s condition, must be carefully monitored to attempt to identify patterns of excessive refill requests.

Benzodiazepines are, at the least, physically addictive in pets. This is a concern only if the pet is on a higher dose every day for a period of weeks. Nevertheless, issues of addiction must be considered over the course of treatment. For some pets, long-term use of benzodiazepines is essential to the resolution of significant phobias. If this is the case, the benzodiazepine should be discontinued via gradual withdrawal rather than abrupt discontinuation. Acute withdrawal of an addicted dog can result in tremors, rigidity, decreased food intake, and convulsions. Acute cessation can cause rebound even in a pet that has not become addicted. In rebound, the original behavior problems return in a more severe manifestation than the original problem. As a result, withdrawal should always be gradual if the pet has been administered a benzodiazepine regularly for more than 1 month.

**Tolerance**

Tolerance can also develop with long-term use of benzodiazepines; that is, steadily increasing doses may be required to achieve a given level of relief from anxiety. This problem is best avoided by a combination approach to long-term resolution of the undesired behavior: appropriate use of behavior modification, environmental management, and drugs other than benzodiazepines that do not produce tolerance.

**SAFETY**

Benzodiazepines are relatively safe drugs in that overdoses must be large to produce life-threatening adverse effects. In cases of accidental massive overdose, administration of activated charcoal within the first 3 hours to adsorb the drug within the gastrointestinal tract and/or induction of vomiting before the onset of sedation can be useful. Flumazenil, a benzodiazepine receptor antagonist, can partially or fully reverse the effects of the drug. It can be given after the benzodiazepine has been absorbed into the body to counteract the effects of the medication. Otherwise, treatment should be supportive, including keeping hypothermic patients in a warm environment and giving IV fluids to speed the rate of elimination of the drug.

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Understanding Behavior (continued from page 529)

In laboratory studies comparing chlordiazepoxide, clonazepam, diazepam, and flurazepam, clonazepam was found to be the safest benzodiazepine for cats, with a dose of greater than 1000 mg/kg PO required to produce fatality. Clonazepam is available in 0.5-mg scored tablets, allowing the very small dosing necessary for a cat and, therefore, can be a good choice for this species. Oxazepam and lorazepam do not have any active, intermediate metabolites and may be considered safer choices than many of the other benzodiazepines for geriatric or obese patients or patients with liver disease. Flurazepam is primarily used to induce sleep.3

CONCLUSION

In all cases for which benzodiazepines are potential drugs of choice, a combination of factors must be considered, including the patient’s age and health, the severity of the animal’s fear, the cost of the medication, the frequency with which the owner can medicate the pet, the size of the animal, and the dose size in which the medication is available. After initial testing, dose size and frequency must be examined regularly and adjusted to obtain the maximum effect with the minimum amount of medication.

REFERENCES