Review Article

TRAZODONE: A POTENTIAL DRUG TO TREAT ANXIETY IN DOGS

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ABSTRACT

Trazodone is a commonly used medication in the United States for the treatment of anxiety in dogs.This article is intended to bring awareness among small animal veterinary practitioners of India about trazodone and its potential uses in the treatment of post-operative hyperactivity, noise phobia, separation anxiety and aggressive behavior.

Keywords: Trazodone, anxiety, dogs

Received : 13.07.2021 Revised : 28.10.2021 Accepted : 28.10.2021

INTRODUCTION

Pet ownership has been increasing over the past decade in India. The era of having pets as only guard dogs has gone, and pets have become a valuable family member. With the increasing urban population, the pets living in apartments are increasing. As veterinarians we are frequently faced with questions about how to deal with behavioral problems like separation anxiety, aggression, destructive chewing, phobias, hyperactivity, and compulsive disorders. Proper training of the pets and seeking the help of a professional dog trainer is useful in many cases. Some of the conditions like anxiety, noise phobia, compulsive disorders, aggression, cognitive functional disorders need behavior modification medications. There are various medications available for treatment of anxiety disorders in canine. In a brief informal online survey done through WhatsApp Veterinarian-groups of the authors, we found that the following drugs are used in India to treat anxiety in dogs: alprazolam, fluoxetine, antihistamines, amitriptyline, gabapentin, acepromazine, herbal products (anxocare, mind calming), phenobarbital and dexmedetomidine oral gel. Surprisingly, we found out that the awareness about the potential uses of trazodone

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in dogs is minimal among field veterinarians. This article reviews trazodone, a drug which has gained much importance and prevalence of use over the past decade in the veterinary practices in US but has not yet been adopted in India.

What is trazodone?

Trazodone is a serotonin antagonist/ reuptake inhibitor (SARI), widely used in human medicine to treat depression, insomnia, and anxiety. It causes sedation at lower doses due to the blocking of the postsynaptic $5HT_{2A}$ receptors, alpha -1 adrenergic receptors and histamine (H1 receptors), and at higher doses it acts as an antidepressant by preventing serotonin reuptake by blocking serotonin transporter (SERT). It also acts as an antagonist at postsynaptic $5HT_{2C}$ receptor (Stahl, 2009). The drug increases the serotonin levels in the body and promotes calmness and reduces anxiety. The drug is primarily metabolized in the liver by cytochrome P4503A4 (Rotzinger *et al.*, 1998). The active metabolite of the drug is chlorophenylpiperazine (mCCP) and is metabolized into inactive compounds by cytochrome P4502D6 and the excretion is mainly renal (70-75%) (Plumb, 2018). Pharmacological studies in small animals are limited. Pharmacokinetic studies in dogs have showed an elimination $t_{1/2}$ of 166 ± 47 minutes and the time to reach peak plasma level was 445 ± 271 minutes after oral administration at a dose of 8 mg/kg (Jay *et al*., 2013). In another study, after rectal administration of trazodone at an approximate dose of 8 mg/kg, the average time to reach peak plasma level was 15 minutes (range 15-30 min) and the elimination $t_{1/2}$ was 12 hours (Interquartile Range, 7.99 to 12.7 hours) (O'Donnell *et al*., 2020).

When to prescribe trazodone?

Trazodone has been used as an adjunctive therapy to improve calming behavior in dogs for more than two decades in the United States (Gruen and Sherman, 2008). It is primarily a drug used in human medicine and adopted into veterinary medicine. Trazodone can be used as a sole agent or combined with other medications to help with fear-free hospital visits, treat anxiety during festival fireworks, thunderstorms, separation anxiety, travel anxiety and to enhance calm behavior in the postoperative period. Trazodone is available as immediate release (regular) and extended release in humans. Presently, the "immediate release" tablets are only used in dogs. The dose recommended in dogs vary from 1.7 to 19.5mg/kg/day (divided q 8-12hrs) and the maximum daily dose described is 600 mg/day, with a maximum individual dose of 300 mg/dose (Gruen and Sherman, 2008).

Use of trazodone during hospital visit

The concept of providing low stress hospital visits is rising in popularity all over the world. Reducing the stress of the pets during hospital visit results in a positive quality experience to the pets, pet parents, veterinary support staff and the veterinarian. In this regard, trazodone is a useful tool in calming down fearful, anxious and aggressive dogs during the visit to the hospital. Trazodone has lessened the stress related behaviors in hospitalized dogs at approximately 90 minutes after administration (Gilbert-Gregory*et al*., 2016). It can be used before the Veterinary hospital visits and is appropriate for long term usage (Lindell, 2018). In dogs experiencing moderate and high scale of fear, anxiety

and stress, trazodone can be given at a dose of 8-10 mg/kg, the night before, and then 2 hours before the hospital visit. Gabapentin at a dose of 20-30 mg/kg can be combined with trazodone if needed (Reck, 2019).

Use in post-operative period

Trazodone can be used in pets with anxiety, and it enhances calm behavior in active dogs during post-surgical recovery (Christensen, 2017). Reduction of hyperactivity during the recovery period helps to reduce the post-operative complications. Gruen *et al*. (2014), used trazodone (3.5 mg/kg every 12 h) along with tramadol (4-6 mg/kg every 8-12 h) for 3 days followed by trazodone alone (7 mg/kg every 12 h) for 4 weeks after orthopedic surgery in dogs. Trazodone was found to promote calmness and improved tolerance to confinement.

Treatment of noise phobia

Noise phobia and anxiety is noticed in many pets during exposure to loud noise from festival fireworks, noise sirens and thunderstorms. Identification of the stimulus, keeping the pet indoors in a soundproof area, desensitization and counterconditioning are other measures that are helpful in reducing the phobia. Medications are needed in pets with severe noise aversion. Trazodone can be given at a dose of 2.8 - 16.5 mg/kg every 12 hours, and a lower dose is recommended when given with selective serotonin reuptake inhibitors or tricyclic antidepressants (Hunthausen, 2019).

Use in separation anxiety

Anxiety due to separation is noticed in some dogs even before or soon after the owner leaves the home. There can be howling, whining, barking, pacing and other destructive behaviors in dogs with separation anxiety. With the increasing nuclear families and apartment living, this behavior can be of concern to the pet owners. Along with behavioral modification therapy, anxiolytic medications also help to reduce the anxiety. Trazodone as a general anti-anxiety medication can be used in the treatment of separation anxiety.

Possible adverse effects of trazodone

Pets must be closely monitored when the drug is administered for the first time for any signs of adverse reaction. Care must be taken in patients with compromised hepatic, renal, cardiac functions, and in glaucoma (Plumb, 2018). It is recommended to start on a lower dose and then increase the dose (Gruen and Sherman, 2008). The side effects described in dogs include aggression, vomiting, gagging, diarrhea, excitability, sedation, increased appetite, behavioral disinhibition (Gilbert-Gregory *et al*., 2016, Gruen and Sherman, 2008). Other reported side effects include hypertension, tachycardia when administered along with tramadol (Borland *et al*., 2015), bradycardia, intraoperative hypotension, priapism (Murphy *et al*., 2017), tremors, ataxia, hypotension and seizures (Wismer, 2000). Transient elevation in heart rate (184.3±8.0 beats/min) was noticed in dogs after intravenous administration and 3 of 6 dogs developed aggression after intravenous administration (Jay *et al*., 2013). Arnold *et al*. (2021) suspected acute hepatotoxicity in a six-year-old dog given trazodone for treatment of separation anxiety. Hepatopathy was resolved in this case once the medication was discontinued.

Trazodone when used along with other serotonergic drugs can cause an increase in the serotonin and can lead to serotonin syndrome. The clinical signs are agitation, tremors, hyperthermia, tachycardia, salivation, diarrhea, dilated pupils, seizures, nystagmus and coma (Mohammad-Zadeh *et al*., 2008, Wismer, 2016). Pets must be monitored for the signs after increase in the dose of the medication or after concurrent use of serotonergic medication. The treatment includes anticonvulsants, muscle relaxants, anti-emetics, IV fluids, symptomatic and supportive care based on the clinical signs noticed (Selman and Millard, 2021). Cyproheptadine, an antihistamine and appetite stimulant drug is a serotonin antagonist and can be given orally or rectally in the management of serotonin syndrome.

Drug interactions

Trazodone is not advised to be used along with monoamine oxidase inhibitors like amitraz, selegiline. Trazodone has potential interaction with the following drugs and should be used with caution. The list includes azole antifungals, fluoroquinolones, macrolide antibiotics, metoclopramide, NSAIDs, cisapride, isoflurane, ondansetron, metoclopramide, digoxin, diuretics, tramadol, phenothiazines and SSRIs (Plumb, 2018).

Currently, trazodone is primarily a human drug that is adopted into Veterinary practices. In the United States, trazadone is used as an off-label medication. In pets we use the immediate release or regular tablets only. Trazodone is available in most of the pharmacies in India, but with the current regulations on the psychoactive medications it may be difficult for a field Veterinarian to get the medication from the pharmacy. Licensing trazodone for veterinary use would help easier access to the medication, aiding better management of anxiety and behavioral disorders in dogs.

CONCLUSION

As Veterinarians, we need to take care of the mental health of our patients. Improving animal welfare includes stressless, fear-free hospital visits, treatment of behavioral disorders, anxiety, and phobia related events. Trazodone can be used in anxious, aggressive dogs before grooming and pedicures. Recently, trazodone has gained popularity as an anxiolytic agent in cats prior to veterinary visit. Identification of the behavioral disorders in pets and treating them effectively using multimodal approach will provide better quality of life to our pets and pet parents.

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