Just Take a Chill Pill

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Why do veterinary patients become stressed or anxious in the hospital setting?

Stressed, anxious and fractious patients often present a significant challenge to the veterinary professional tasked with providing their care. Safety for both veterinary staff members, and the patients themselves can be difficult to maintain when dogs and cats enter the hospital setting in a stressed, anxious or fear aggressive state. Many of these patients present in this manner because of a past negative experience associated with a veterinary visit. A study completed in 2009, out of Germany, showed that 78.5% of dogs in the study demonstrated fear during their physical exam, less than half of these dogs remained calm and 13.3% were either carried or dragged into the hospital for the appointment. This has a two-fold effect in veterinary medicine. The stress on the animal can have a negative impact on the owners as well. This often results in delayed medical and surgical care for these patients, in order to avoid the emotional challenge that comes with seeing their pet struggle with anxiety and/or fear. Existing evidence correlates this struggle for dogs and cats, with their initial puppy or kitten visit.

It is paramount to establish the difference between fear and anxiety, recognize how fear becomes the causation of anxiety, and act as a team to minimize the negative experience as best as possible. Fear is a safety mechanism that has evolutionarily helped animals survive immediate threats to life. When an animal perceives a situation as dangerous, the sympathetic nervous system activates to help the animal escape the threatening stimulus. This is known as the fight or flight response. Anxiety occurs when an animal anticipates a situation as one that is threatening to life (whether real or imagined). Anxiety stems from repeated exposure to stimuli that trigger the fight or flight response. An example of this is the feline patient who becomes anxious at the simple sight of the cat carrier while in the home. The association between the carrier and a negative experience, imprints on the cat and signals a warning sign to the brain that danger is present.

Physiological impacts of the response to stress

The sympathetic nervous system serves as the branch of the autonomic nervous system responsible for activating the fight or flight response. The stress signal originates in the amygdala of the brain and initiates a response in the hypothalamus. This in turn activates the pituitary gland and adrenal gland simultaneously, resulting in the release of the hormones ACTH and epinephrine. The release of these hormones results in the production of cortisol, another hormone, that increases blood pressure, blood glucose and results in immune system suppression. This is the body's attempt to increase energy in order to escape the threat. Physiologically, this boost of energy is the result of liver cells bound to epinephrine resulting in the production of glucose. The production of cortisol will create energy from fatty acid production in order to activate muscle tissue to respond. Catecholamine release will cause an increase in heart rate, an increase in respiratory rate, vasoconstriction, vasodilation in muscle tissue,

mydriasis, absent or slowed digestion, inhibition of tear and saliva production, loss of peripheral vision, loss of hearing, decreased spinal reflexes, and relaxation of the bladder. When this response persists repeatedly or chronically, it can become life threatening.

Negative impacts of anxiety and/or fear during general anesthesia and recovery from surgery

Aside from analgesia and amnesia, an additional goal with any anesthetic event is to maintain and preserve homeostasis as much as possible. The overall resulting increase in heart rate and vasoconstriction (elevated blood pressure) from catecholamine release in the stressed patient, will increase cardiac workload and thus increase myocardial oxygen demand. An increase in respiratory rate (panting) can lead to increased work of breathing, hypocapnia, and reduced effective gas exchange. A reduction in effective gas exchange will often times require a higher vaporizer for maintenance anesthesia. Higher inhalant settings on the vaporizer can lead to an increase in dose dependent side effects. Additionally, anxious, and/or fearful patients will often have required larger doses of pre-medications and induction drugs to reduce MAC. This can have dose dependent adverse side effects as well.

Secondly, evidence across the board in both human and animal models, suggests that stress directly impacts wound healing. Stress can lead to increased local cytokine release and increase glucocorticoid production both of which will diminish the body's ability to heal. Delayed wound healing from a surgical procedure or injury can lead to a higher rate of complications such as wound infection, wound hypoxia, and central neuronal sensitization (wind-up pain). This will often result in longer hospital stays or necessitate re-admit to the hospital. A peer-reviewed study published by Brain, Behavior, and Immunity in 1998 showed that mice subjected to stress with restraint, healed 27% slower than their counterparts not exposed to the same stimulus.

How can we reduce or eliminate activation of the stress response?

In addition to well-known and frequently utilized fear-free environmental modifications, the use of anxiolytic agents and sedatives that can be administered at home prior to the patient's arrival at the veterinary hospital, can reduce or eliminate anxiety, fear and fear-based aggression. In March of 2020, the American Animal Hospital Association (AAHA) released updated anesthesia monitoring guidelines for dogs and cats. In these guidelines, temperament is included as a necessary point of consideration during the pre-anesthetic evaluation. Further, anxiety is listed as a preanesthetic condition deemed "advisable to critical" to correct prior to general anesthesia. A common and important concept with any anesthetic event, is the use of a balanced anesthesia protocol. This should apply to all four phases of anesthesia: pre-anesthesia, induction, maintenance, and recovery. The authors of these guidelines suggest that anesthesia begins at home and that the use of pre-admit oral sedation should be considered part of a balanced pre-anesthesia protocol. In order to achieve the desired effect, these drugs should be administered at home, prior to travel/arrival and therefore prior to activation of the stress response.

Common pre-admit oral anxiolytic agents and sedatives

Gabapentin: Gabapentin has been used previously in human medicine as an anticonvulsant. It has gained popularity in veterinary medicine as an analgesic specifically targeting nerve pain. Sedation is one of the most common side effects of gabapentin administration in dogs and cats. In the initial period of administration, the sedation side effect may be more profound. This, combined with the high margin of safety of gabapentin, makes it an ideal choice to use alone or in combination with other agents. Dosing for gabapentin is often 10mg/kg but can safely be administered at higher doses (up to 20mg/kg) at the discretion of the attending veterinarian. In addition to co-existing disease, dosing considerations should include whether or not gabapentin will be the sole agent versus used in combination. Contraindications include pediatric patients and liver failure. Caution should be used in the critical patient. Typically, administration should occur at home the night before admit and the morning prior to admit (2 hours minimum prior to admit).

Trazodone: Trazodone has historically been used as an anxiolytic and sleep aid in human medicine. Due to the side effect of sedation, it has become a staple in anxious veterinary patients and patients on activity restriction post-surgery. It is classified as a serotonin antagonist and reuptake inhibitor (SARI). Dosing in dogs is generally 5-8mg/kg and can take an hour or more to have full effect. In the cat a dose of 50-75mg per cat is often utilized. As with gabapentin, consideration of other agents administered to the patient, should be given when determining appropriate dosing. Trazodone can cause varied levels of sedation in each individual patient. Caution should be used in patients with cardiovascular disease with existing arrythmias. Patients taking monoamine oxidase inhibitors (MAOI) should not receive trazodone. Additionally, trazodone should be administered very cautiously in patients receiving CBD oil due to the increased risk of serotonin syndrome.

Acepromazine: Acepromazine is a phenothiazine tranquilizer that has been widely used in veterinary medicine as part of a balanced anesthetic protocol. The oral tablet form of acepromazine is often used for at home behavior modification but has historically been unreliable with consistency in dosing. Use of the injectable form applied oral transmucosally (OTM), will produce moderate sedation in a much more reasonable time frame (20-30 minutes). The dose range for OTM acepromazine is similar to injectable dosing at 0.01-0.05mg/kg. In the patient that is highly aggressive, dosing should be administered about an hour prior to admit. Contraindications include cardiovascular disease, liver failure, renal disease, geriatric patients, and pediatric patients.

Melatonin: Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. The pineal gland regulates sleep by delivering more melatonin at night and less during the daytime. It can be safely utilized in veterinary patients and has no absolute contraindications. Dosing is usually determined by weight range. For patients less than 5kg, administer 1mg. For patient 5-15kg, administer 1.5mg. For patients 15-50 kg, administer 3mg. For patients more than 50kg, administer 5 mg. Melatonin may be purchased over the counter, however, should clients choose this option careful examination of the ingredient list is required. Some melatonin products marked towards people contain xylitol.

Examples of protocols and timing

Gabapentin + Trazodone: Administer a dose of each the evening prior to and morning of admit. Timing should be determined based on drop off time. Generally, patients dropping off at 8am should receive a dose at 6pm the night before and 6am the morning of.

"**The Chill Protocol":** The chill protocol refers to the use of gabapentin, melatonin and OTM acepromazine administered in conjunction and at specific times prior to admit. The protocol was developed by clinicians at Cummings School of Veterinary Medicine at Tufts University. It has been routinely utilized in dogs and cats prior to admit to their teaching hospital since 2014. In May of 2019, Clinicians Brief published an article detailing the use of this protocol in an aggressive canine patient. The chill protocol consists of administration of gabapentin PO (20-25mg/kg) about 12 hours prior to admit, gabapentin (20-25mg/kg) and melatonin (doses as listed above) PO 1-2 hours prior to admit, and OTM acepromazine (doses listed above) 30 minutes before scheduled arrival at the hospital.

Owner education and compliance

The use of a pre-admit oral sedation protocol, allows pet owners to feel more involved in the overall care and well-being of their pet. Owner compliance with administering these medications will directly impact efficacy of each protocol. The entire veterinary team should work together to educate clients on expected degrees of sedation. Specifically, that sedation will appear more profound at home versus when the animal enters the hospital setting. Trail runs at home can be useful to determine patient specific dosing needs prior to the day of admit. Additionally, clients should be made aware of the importance of proper timing of administration of to achieve desired effect. Creating medication schedulers to go home with the client may serve as a useful reference tool for pet owners.

References:

Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. *Immunol Allergy Clin North Am*. 2011;31(1):81-93. doi:10.1016/j.iac.2010.09.010

Padgett DA, Marucha PT, Sheridan JF. Restraint stress slows cutaneous wound healing in mice. *Brain Behav Immun*. 1998;12(1):64-73. doi:10.1006/brbi.1997.0512

Grubb T, Sager J, Gaynor JS, Montgomery E, Parker JA, Shafford S, Tearney C. Anesthesia and Monitoring Guidelines for Dogs and Cats. *J Am Anim Hosp Assoc* 2020; 56: DOI 10.5326/JAAHA-MS-7055)

Costa RS, Karas AZ, Borns-Weil S. Chill Protocol to Manage Aggressive and Fearful Dogs. *Clinicians Brief.* May 2019. Accessed March 2020. https://www.cliniciansbrief.com/article/chill-protocol-manage-aggressive-fearful-dogs

Lloyd JKF. Minimising Stress for Patients in the Veterinary Hospital: Why It Is Important and What Can Be Done about It. *Vet Sci*. 2017;4(2):22. Published 2017 Apr 13. doi:10.3390/vetsci4020022

Cummings A. Pre-hospital Sedation Options for Aggressive and Anxious Dogs. *MSPCA Angell.* Accessed July 2020. https://www.mspca.org/angell_services/pre-hospital-sedation-options-for-aggressive-and-anxious-dogs

Orlando JM, Case BC, Thomson AE, Griffith E, Sherman BL. Use of oral trazodone for sedation in cats: a pilot study. *J Feline Med Surg*. 2016;18(6):476-482. doi:10.1177/1098612X15587956