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The use of desmopressin acetate to reduce polyuria and polydipsia associated with prednisolone administration

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Glucocorticoids are used for many purposes in veterinary medicine but often come with significant adverse effects. Polyuria and polydipsia are the most common adverse effects noted by owners. To determine whether administration of desmopressin ameliorated the polyuria and polydipsia, a prospective study with 7 healthy Walker Hounds was performed. Daily water intake and urine specific gravity were measured in dogs under 4 separate conditions: no medications, prednisolone only, prednisolone and desmopressin, and prednisolone immediately after discontinuation of desmopressin. When compared to baseline, six out of seven dogs became polydipsic after administration of prednisolone twice daily. When desmopressin was administered to dogs receiving prednisolone, there was a statistically significant decrease in water intake and sodium concentration, and a significant increase in urine specific gravity. This suggests that desmopressin ameliorates the most significant side

effect of prednisolone noted by owners, but that hyponatremia is an important complication associated with desmopressin.

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CHAPTER I

INTRODUCTION

Steroids, particularly prednisone and prednisolone, are used extensively in veterinary medicine. Their use is so universal that it is difficult to identify a practitioner who is uncomfortable prescribing them. It is important, however, to remain vigilant in prescribing these medications as their use is not benign.

The side effects of steroids are vast and have the potential to affect almost every body system. Some of the most well-known and commonly encountered adverse effects include polyuria, polydipsia, and polyphagia. These are experienced by 90.4%, 88.5%, and 86.5%, respectively, of dogs in one study (Lau et al., 2019) in which dogs were treated with high doses of steroids for management of steroid-responsive meningitis-arteritis.

Issues such as gastrointestinal ulceration, renal and hepatic damage, and increased risk of infection are examples of side effects that are not likely to be apparent to owners until they are well-established. In the authors' experience, the cost of treating these adverse effects once they are established may be substantial enough that humane euthanasia is chosen as an alternative to treatment.

Behavioral changes may also be seen. When the owners of 31 mixed breed dogs were surveyed, changes such as increased aggression, increased propensity to startle or bark, and food

guarding were reported (Notari & Mills, 2011). In a review by Lambert et. al (Lambert, Coe, Niel, Dewey, & Sargeant, 2015), behavioral issues were cited as the first or second reason for pet dogs being surrendered to shelters. These surrendered pets may end up being euthanized as behavioral problems are cited as the sole reason for euthanasia in 9.6 to 17.8% of cases (Lambert et al., 2015).

For some owners, the side effects can become so bothersome that owners report a decrease in dogs' quality of life. In Lau et. al, owners of dogs being treated for steroid-responsive meningitis-arteritis were asked to rate quality of life during treatment. Owners reported that higher prednisone doses were associated with more severe side effects. In addition, quality of life was significantly worse during treatment compared to that during clinical resolution. For many pet owners, this would be deemed unacceptable as domesticated dogs for whom owners seek veterinary care are often considered members of the family.

Desmopressin acetate, an analogue of the hormone vasopressin, has been utilized in human medicine for many specific reasons. One of these reasons is the treatment of bed wetting in children, in which intranasal or oral administration prior to bedtime successfully prevented enuresis in almost 90% of patients (Chiozza et al., n.d.; Del Gado et al., 2005). This drug has been used in veterinary medicine, though primarily for the treatment of central diabetes insipidus. Investigation into its use in reducing urine volume has not been previously investigated and may present a solution to the issue of extreme polyuria and polydipsia experienced secondary to prednisone therapy while allowing the pet to remain on doses that are effective for controlling the disease for which corticosteroid therapy is indicated.

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CHAPTER II

LITERATURE REVIEW

Vasopressin

Vasopressin is a hormone synthesized by magnocellular neurons in the posterior hypothalamus, also known as the neurohypophysis. One of the primary functions of vasopressin is to regulate extracellular fluid volume by regulating renal handling of water. Vasopressin is the key antidiuretic hormone (ADH) in all mammals. Release of vasopressin is triggered by both hypovolemia and hypernatremia (Cuzzo, Padala, & Lappin, 2020). An increase in plasma osmolality by as little as 1%, or a decrease in blood volume or blood pressure by 10 to 15%, is sufficient to trigger osmoreceptors in or near the hypothalamus (I. Campbell, 2011; Nelson, 2015a). A drop in blood pressure results in a decrease in atrial pressure, leading to decreased stretch of baroreceptors located in the carotid bodies, aorta, and lungs(I. Campbell, 2011; Nelson, 2015a). Both of these scenarios trigger the generation of vasopressin in the cell bodies of the magnocellular neurons (I. Campbell, 2011; Nelson, 2015a).

Antidiuretic actions are mediated through V_2 cyclic adenosine monophosphate (cAMP)-dependent receptors on renal collecting ducts (I. Campbell, 2011; Nelson, 2015a). Vasopressin increases the permeability of the collecting duct to water by inserting aquaporin-2 water channels into the apical membrane of the epithelial cells lining the collecting ducts, thereby allowing an osmotic equilibrium to form between the urine and the hypertonic medullary

interstitium (Nelson, 2015a). In this way, the amount of water absorbed by the collecting duct is increased and the amount lost in the urine is decreased. Once vasopressin separates from the V_2 receptor, intracellular cAMP levels decrease and the aquaporin-2 channels are internalized(Nelson, 2015a).

Other vasopressin receptors include V_{1a} and V_3 (or V_{1b}), which are responsible for vasopressin's other functions, vasoconstrictive actions (pressor effects) and stimulation of ACTH from the anterior pituitary, respectively (Nelson, 2015a).

Desmopressin

Desmopressin acetate (DDAVP) is a synthetic commercially available analogue of vasopressin, with a strong affinity for V_2 receptors (Del Gado et al., 2005). Desmopressin is formed when d-arginine is substituted for l-arginine present on vasopressin, and the terminal amino group is removed from the cysteine molecule. These modifications increase the antidiuretic effects of vasopressin while decreasing the pressor effects (Sawyer, Acosta, & Manning, 1974).

DDAVP has many therapeutic uses in both human and veterinary medicine, including but not limited to the treatment of central diabetes insipidus, bed wetting in children, and von Willebrand disease. However, desmopressin must be used with care, as hyponatremia is recognized as a potentially serious side effect.

Hyponatremia is a well-known side effect in people receiving desmopressin for treatment of central diabetes insipidus(Behan et al., 2015; Hossain, Ghazipura, Reddy, Rivera, &

Mukherjee, 2018; Stoof, Cnossen, de Maat, Leebeek, & Kruip, 2016; Wang, Lin, Huang, & Chang, 2011). This occurs due to the retention of water in the extracellular fluid, which acts to dilute the sodium within the bloodstream. Clinical signs are not typically encountered unless serum sodium is less than 120mEq/L, or unless the decrease has occurred quickly (Burkitt Creedon, 2014). Any cell that contains sodium-potassium ATPase pumps will swell as water moves from the hypoosmolar extracellular fluid into the relatively hyperosmolar interior of the cell (Burkitt Creedon, 2014). While this change occurs in many cells throughout the body, the central nervous system is most sensitive. Once hyponatremia has existed for more than two to three days, it is considered chronic and osmotically active substances such as potassium and amino acids are extruded from cells(Dewey, 2016). Overly aggressive correction of chronic hyponatremia then leads to axonal shrinkage and subsequent demyelination(Dewey, 2016). The lesions of myelinolysis may not be evident for several days after correction of hyponatremia. There is myelin loss and injury to the oligodendroglial cells in the pons, thalamus, subcortical white matter, and cerebellum(DiBartola, 2012). Seizures, coma, or even death may occur as a result(Burkitt Creedon, 2014).

Case reports of these severe side effects include a 6-year-old boy who experienced generalized convulsions with unconsciousness, a tonic-clonic pattern of movements and cyanosis on the fourth day of DDAVP therapy for nocturnal enuresis (Schwab et al., 1996). This individual had a severe hyponatremia of 125 mmol/L at initial evaluation but this later normalized. Though this individual required intubation and ventilation, he was extubated and

recovered successfully. Alternative therapy was initiated for his nocturnal enuresis. This case highlights the risk assoiated with therapeutic use of DDAVP.

A second case report(Hossain et al., 2018) describes a 69-year-old man who presented to the emergency department with a one month history of progressive fatigue, anorexia, dizziness, weakness, and gait instability. This individual was being treated with desmopressin at 10 μg twice daily for central diabetes insipidus. At initial examination, serum sodium was 96 mmol/L, representing a decrease from 125 mmol/L 2.5 months prior to presentation, and also down from 134 mmol/L when desmopressin therapy was initiated 6 months prior. Over the course of 8 days of hospitalization, serum sodium levels stabilized between 130 and 132 mmol/L and mental status and neurologic symptoms improved. Magnetic resonance imaging (MRI) of the brain performed 25 days after admission, however, revealed central pontine myelinolysis which was not present on MRI on day 3 of hospitalization. The authors speculate that despite the slow correction of hyponatremia, abrupt discontinuation of the individual's desmopressin may have had an adverse effect and recommend tapering the drug in future cases.

Interestingly, reports such as these have appeared with decreasing frequency since the 1990s, likely indicating an increased knowledge and subsequent avoidance.

Conditions Treated with Desmopressin

Diabetes insipidus

Diabetes insipidus is the disease resulting from decreased production or action of vasopressin. Central diabetes insipidus (CDI) is the manifestation of destruction or failure of production of the magnocellular neurons that secrete vasopressin. It can be caused by destruction of the production sites of ADH in the hypothalamus (ie the supraoptic and paraventricular nuclei), loss of the axons that carry it to its storage sites in the posterior pituitary, or disruption of the ability to release ADH(Engelking, 2012; Hall, 2016; Nelson, 2015b). In essence, any sort of damage to the brain including external trauma or destruction of neural tissue secondary to neoplasia, infection, or disrupted blood supply(Engelking, 2012; Hall, 2016; Nelson, 2015b) may lead to CDI. In people, CDI occurs in 26-28% of cases of moderate to severe traumatic brain injury (Agha et al., 2004). Though this is a rare phenomenon in veterinary medicine, it has also been reported in dogs and cats following traumatic brain injury (Foley, Bracker, & Drellich, 2009) (F. E. Campbell & Bredhauer, 2005). Other commonly recognized causes of CDI in veterinary medicine include neoplasia, hypothalamic or pituitary malformation, cysts, lymphocytic hypophysitis, migration of parasites, and hypophysectomy (Nelson, 2015a).

In both human and veterinary medicine, supplementation with DDAVP is the standard of care for CDI. It is available as tablets, injectable solution, and an intranasal spray, which is commonly administered in the conjunctival sac of affected dogs for owner convenience. Since CDI is rare in dogs, there is no universally accepted treatment protocol. Alterations in dose are

often made based on the individual's response. If treatment with DDAVP cannot be provided, dogs with CDI may have an acceptable quality of life as long as they are provided free access to water and access to a place to urinate.

Diabetes insipidus may also be nephrogenic in origin and is, in those cases, identified by that qualifying adjective. Nephrogenic diabetes insipidus is a form of the disease in which there is a deficiency or complete lack of interaction between vasopressin and its receptors on the renal tubules(Nelson, 2015a). In veterinary medicine, nephrogenic diabetes insipidus most often occurs secondary to other disorders (Cohen & Post, 2002), such as hyperadrenocorticism, pyometra, pyelonephritis, and hypercalcemia. For example, in cases of hypercalcemia, diabetes insipidus is believed to be caused by damage to ADH receptors located on the membranes of the renal collecting ducts. Therefore, in hypercalcemia, as well as the other causes listed above, treatment of the underlying disease is the most appropriate management option. Further discussion of acquired nephrogenic diabetes insipidus will not be included. We will, however, discuss some of the lesser known applications of DDAVP.

Nocturia

One of the most common uses of DDAVP in human medicine is for treatment of nocturia, which is defined as 2 or more episodes of urination during normal sleeping hours. Nocturia is estimated to affect 15.5% of men and 20.9% of women (Kupelian et al., 2011). A more specific term, enuresis, refers to the transitory urinary incontinence that most frequently affects young children before adequate control of urinary sphincters is achieved. Nocturnal

enuresis is not exclusively a disorder of young children, and persists beyond 6 years of age in approximately 10% of children (Del Gado et al., 2005). Pharmacologic treatment options include imipramine, a tricyclic antidepressant (Fritz, Rockney, & Yeung, 1994), while alternative management options include restriction of fluid intake in the hours before bedtime and the use of an enuresis alarm (Nevéus et al., 2020). Finally, DDAVP has evolved as an effective pharmacologic treatment option for nocturnal enuresis, and has been in use for more than 20 years (Del Gado et al., 2005).

Efficacy of DDAVP for treatment of nocturia

In a study by Chiozza and others (Chiozza et al., 1999) involving Italian children aged 5 to 17 years, intranasal administration of DDAVP was used in 5 different treatment schedules. The first 2 groups involved administration of DDAVP at doses of 20mcg/day and 30mcg/day at bedtime for 6 weeks. In groups 3 and 4, DDAVP was administered at 20mcg and 30mcg, respectively, for the first two weeks. A 2-week washout period then followed, after which group 3 received 30mcg and group 4 received 20mcg. For group 5, DDAVP was administered at increasing dosages, from a minimum of 20mcg to a maximum of 40mcg to assess response in relation to dose. For each group, efficacy was assessed via recording the number of nights that passed without any involuntary urination. In the first two groups, there was a significant decrease in the number of “wet nights”. This held true for the third and fourth groups as well. In fact, although interruption of therapy during the 2-week washout periods lead to an increase in the number of “wet nights,” the incidence still remained lower than that in the baseline

periods before the study was commenced, and in the follow-up periods. There was no significant difference between efficacy for those groups that received 20 mcg/day and those that received 30 mcg/day. Treatment was also deemed safe, although serum electrolytes were not monitored, as only 3 of 218 patients experienced side effects, including local irritation in 2 patients and rhinitis in 1.

Efficacy of DDAVP for treatment of enuresis was demonstrated in a second study by Del Gado et.al, which investigated DDAVP use in either intranasal or oral forms in 541 patients. Success was defined as resolution of enuresis within 6 months, and was achieved in 89.6% of participants. An additional 4.4% were considered partial responders, defined as a reduction of more than 50% but less than 90% in the number of wet nights. Urine volume was not measured in this study, however.Only 5. 9% of the total numbers of participants experienced side effects. Serum levels of sodium, potassium, and chloride were within respective reference ranges both at baseline and at the end of treatment. This is an important finding because hyponatremia is arguably the greatest risk associated with the use of DDAVP.

Von Willebrand Disease

Von Willebrand disease (vWD) is the most common inherited bleeding disorder in both humans (Swami & Kaur, 2017) and dogs (Thomas, 1996), and was first described by Dr. Eric von Willebrand in 1926. The affected individual was a 13-year-old female in which excessive hemorrhage during a menstrual period lead to her demise (von Willebrand, 1926). vWD results from deficient or defective plasma levels of von Willebrand factor (vWF), which is produced by

megakaryocytes and endothelial cells. In endothelial cells, vWF is stored in cytoplasmic granules known as Weibal-Palade bodies and in the alpha granules of platelets. The disease exists as three different types. Type 1 is the most common in man (Swami & Kaur, 2017) and dogs (Callan, Gigers, & Catalfamo, 2005), and is characterized by a decrease in the concentration of vWF to <50% of reference ranges. vWD affects approximately half of Doberman Pinschers, and has been reported in more than seventy other breeds (Callan et al., 2005). These individuals may be asymptomatic or have only mild signs of mucocutaneous bleeding. In type 2 vWD, there is a qualitative deficiency of vWF activity.

DDAVP for von Willebrand disease

In humans with vWD, administration of desmopressin results in an increase in both factor 8 and vWF. This is proposed to be due to the release of vWF from endothelial cell Weibel-Palade bodies. A series of studies by Mannucci et al. revealed a 2- to 5-fold increase with DDAVP in vWF in normal adults and those with type-1 vWD (Mannucci, Canciani, Rota, & Donovan, 1981; Mannucci, Pareti, Ruggeri, & Capitanio, 1977). Another study performed at Harvard Medical School supported these results, and also determined that levels of vWF were highest at 60 minutes post-DDAVP injection(Guddati, Rosovsky, Van Cott, & Kuter, 2019). In dogs, however, there was no statistically significant increase in vWF after desmopressin administration in healthy dogs or Doberman Pinschers with von Willebrand's disease (Giger & Dodds, 1989). In addition, there was no substantial change in factor 8 activity up to 6 hours

after subcutaneous DDAVP administration (Mansell & Parry, 1991). Therefore, the therapeutic use of DDAVP in canine vWD is rather limited.

This finding was echoed in a 2002 study performed by the University of Pennsylvania in which administration of DDAVP at a dose of 1 µg/kg subcutaneously did not elevate levels of vWF to within reference range in any of the sixteen dogs tested. In addition, when hemostasis was evaluated in this same group of dogs by buccal mucosal bleeding time and PFA-100®, although there was a significant decrease in both parameters, neither of which resulted in values within reference range (Callan & Giger, 2002). This suggests that procedures with the potential to cause hemorrhage would not be safe in DDAVP-treated individuals with vWD.

Mammary carcinoma

There was once interest in DDAVP as supplemental treatment for mammary carcinoma when it was determined that DDAVP inhibited lung colonization by aggressive carcinoma cells *in vitro* (Alonso, Skilton, Farïas, Bal De Kier Joffé, & Gomez, 1999). In an attempt to evaluate these results in canine veterinary medicine, DDAVP was administered in a similar fashion (intravenously 30 minutes prior to and 24 hours following surgery) to bitches undergoing surgical resection of stage 3 or 4 mammary gland tumors(Hermo et al., 2008). When mammary carcinomas were evaluated separately, both median disease-free time and overall survival times were >600 days in the DDAVP versus 97 days and 351 days for the placebo group, respectively. Unfortunately, these findings were contradicted in the most recent study to address this question. When 24 dogs with mammary carcinomas were split into equal groups of

12 each, there was no difference in time to metastasis or overall survival between those who received DDAVP at 3mcg/kg subcutaneously as part of their anesthestic pre-medication and then again 24 hours post-operatively, and those who received a placebo(Sorenmo, Durham, Evans, Scavello, & Stefanovski, 2020)

Corticosteroids

Steroid hormones are produced by the three layers of the adrenal cortex: the zona glomerulosa, zona fasciculata, and zona reticularis. Aldosterone is the main product of the zona glomerulosa, although it may also produce corticosterone (I. Campbell, 2011). Cortisol is the main product of the zona fasciculata. Androgens, mainly dehydroepiandrosterone and andreostenedione, are the main products of the innermost zona reticularis. Cholesterol is the main precursor of all adrenal steroids and is provided to the adrenal gland from the source of low-density lipoproteins via receptors located on adrenal tissue (Arlt & Stewart, 2005).

Exogenous glucocorticoid therapy is widely used in both human and veterinary medicine. Glucocorticoid use primarily falls into one of three modalities: anti-inflammatory, immunosuppressive, and replacement therapy in the case of hypoadrenocorticism. Glucocorticoids act through intracellular receptors of the steroid receptor superfamily and through membrane-bound receptors that are located on most cells in the body (Thacker, 2010). Glucocorticoids exert anti-inflammatory activity by reducing the production of several interleukins, including IL-3, IL-4, IL-5, and IL-10, tumor necrosis factor alpha, and granulocyte monocyte colony stimulating factor (Thacker, 2010).When used at immunosuppressive doses,

glucocorticoids also decrease phagocytosis and IL-1 production by macrophages, decrease antigen presentation, and reduce extravasation of white blood cells, including the margination and migration of neutrophils (Viviano, 2013).

Because of these varied mechanisms, the use of steroids has become the mainstay of treatment for many immune-mediated disorders, including primary immune-mediated anemia, primary immune-mediated thrombocytopenia, idiopathic immune-mediated polyarthritis, and steroid-responsive meningitis-arteritis. However, there are drawbacks associated with this treatment, including side effects such as polyuria and polydipsia, which are observed in approximately 90% of dogs (Lau et al., 2019).

Although it is common for other immunosuppressive agents to be used concurrently with glucocorticoids in order to allow for more rapid tapering of glucocorticoid doses, considerations such as the high cost of modified cyclosporine (approx. $200 per month for a dog weighing 25 kilograms), the gastrointestinal side effects of mycophenolate, and the need for monitoring of liver enzymes with azathioprine can make the use of secondary immunosuppressive medications impractical and expensive. The cost of DDAVP is $50-100 for five milliliters of the 0.01% intranasal preparation. If dosed similarly to the doses used in our study, this amount would be sufficient to treat a 25kg dog for over 3 months. In addition, if a future study reveals that oral DDAVP is also efficacious in dogs, tablets are available at an even lower cost.

Steroid side effects continue to be an issue with pets and pet owners. For some, steroid side effects may culminate in pets being surrendered to shelters and may end up with euthanasia, as disease accounts for 21 to 63% of shelter euthanasias (Lambert, Coe, Niel, Dewey, & Sargeant, 2015).

Understanding the mechanism of polyuria and polydipsia with glucocorticoid is paramount to trying to dampen it. Proposed mechanisms include primary polydipsia, antagonism of the anti-diuretic hormone (ADH) receptor (Nelson, 2015a; Reusch, 2015), and inhibition of ADH release from the pituitary(Reusch, 2015). This last theory is supported by research performed by Papanek and Raff(Papanek & Raff, 1994) in which 5 healthy dogs received continuous infusions of either hypertonic saline or cortisol in sequential protocols. Arterial blood samples were obtained to measure hematocrit, plasma sodium, plasma potassium proteins, vasopression, cortisol, and osmolality. The results indicated that infusion of cortisol caused a significantly decreased vasopressin concentration on days 4 and 7 when compared to the control period. The authors speculate that cortisol directly inhibits vasopressin release or suppression of vasopressin from magnocellular cells, similar to the case in central diabetes insipidus. They also speculate that cortisol may induce changes at the osmoreceptor.

Due to the success of DDAVP in reducing urine volume in nocturia and the other indications described above, my thesis research was designed to determine whether its use would be efficacious in reducing polyuria and polydipsia in dogs being treated with corticosteroids. If the theory of Papanek and Raff holds true and there is corticosteroid-induced inhibition of vasopressin release or synthesis, we would expect DDAVP to be effective. We

specifically investigated the use of subcutaneous administration of DDAVP. Although DDAVP is available in both tablet forms and as eye drops for subconjunctival application, and these are likely to be more convenient for owners, tablet forms were purposefilly avoided in this study due to the fact that oral hormones in dogs typically have poor bioavailability compared to bioavailabity in people. In regards to ocular administration, it has been my mentors' experience that subcutaneous administration leads to more consistent absorption when compared to the subconjunctival route.

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CHAPTER III

EFFECTS OF DESMOPRESSIN ACETATE ADMINISTRATION IN HEALTHY DOGS RECEIVING PREDNISOLONE

Introduction

Glucocorticoids, including prednisolone, are used in the treatment of many diseases in veterinary medicine (Elkholly et al., 2020)(Blois & Matthews, 2017)(Archer, 2017). These include, but are not limited to, dermatologic diseases in which anti-inflammatory effects are beneficial in providing patient comfort, as well as immune-mediated diseases in which higher doses are used for immunosuppression (Reusch, 2015)(Archer, 2017). Anti-inflammatory activity is mediated mainly through reducing the production of several interleukins. When used at immunosuppressive doses, glucocorticoids exert their activity by decreasing phagocytosis and IL-1 production by macrophages, decreasing antigen presentation, and reducing extravasation of white blood cells (Viviano, 2013)(Whitley & Day, 2011)(Reusch, 2015)(Archer, 2017). Like any drug, however, glucocorticoids have adverse effects, including polyphagia, muscle wasting, and, perhaps most bothersome to owners, polyuria and polydipsia (Archer, 2017; Elkholly et al., 2020; Goggs, 2020; Whitley & Day, 2011). For many, these may become a quality of life issue for both owners and their pets (Lau et al., 2019). Because these side effects are dose-related, owners may independently decrease dosages or discontinue medications in

order to alleviate side effects. Doing so, however, can lead to a lack of treatment response or disease relapse.

Proposed mechanisms for the polyuria and polydipsia induced by glucocorticoids include primary polydipsia and antagonism of the anti-diuretic hormone (ADH) receptor (Nelson, 2003)(Reusch, 2015). ADH, or arginine vasopressin, is a peptide hormone secreted by the posterior pituitary gland to maintain homeostasis regarding extracellular fluid osmolality and blood pressure and volume (Nelson, 2015). Its main action is to promote reabsorption of free water in the collecting ducts of the kidneys. Following binding of ADH to the V2 receptors on the basolateral membrane of renal tubular cells in the collecting duct epithelia, water channels (aquaporin-2) are inserted into the apical membrane, allowing free water to enter the cell and then diffuse down its concentration gradient into the medullary interstitium. The net effects include free water being extracted from the glomerular filtrate, resulting in a decrease in urine volume and an increase in urine concentration.

Desmopressin, a synthetic analogue of ADH, has been used to treat central diabetes insipidus, a disease in which ADH production is deficient (Nelson, 2015). It has also been used successfully in the treatment of nocturia in children (VANDE WALLE et al., 2006), most often by oral administration sixty minutes prior to bedtime (Nevéus et al., 2020). The efficacy is often evident immediately, and approximately 2/3 of children will have an intermediate to full response (Robson, Nørgaard, & Leung, 1996). To the authors' knowledge, however, its use as an adjunctive treatment to decrease polyuria and polydipsia in dogs being treated with exogenous glucocorticoids has not yet been explored.

The aim of this study was to determine whether concurrent administration of desmopressin during prednisolone therapy would lead to a decrease in water consumption and increase in urine specific gravity. A secondary aim was to assess the safety of administration of desmopressin, specifically in relation to serum sodium concentrations.

Materials and methods

Study design

Experiment and animal care protocols were approved by Mississippi State University Institutional Animal Care and Use Committee. Mississippi State University is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care.

Seven adult Walker hounds, members of a healthy research dog colony, underwent screening prior to drug administration via a full physical exam as well as a CBC, chemistry, and urinalysis; no significant clinical abnormalities were identified. In one dog, a urine specific gravity (USG) rather than a full urinalysis was performed due to insufficient sample quantity. Water intake per day and USG once daily (at noon) were measured for each dog. To measure the water intake per day, a large water bowl (secured to the chain linked walls of the run) was filled with a known amount of water measured with a large, graduated cylinder. Each morning, the water left in the bowl was measured to determine the amount drunk in the previous 24 hours, and the bowl refilled with a known amount of water. In addition to urinating in their kennels and while walked in the morning and evening, the dogs were walked within one hour of noon daily, and a body weight and free catch urine sample collected. If urine could not be

collected at this time, it was obtained either during an addition walk prior to 5 pm, or from a sample collected from the floor in the dog's run. The USG was measured on these noon samples with a standard refractometer (Reichert Vet 360). These procedures were followed for 5 days prior to administration of any medication to the dogs. This period was considered the control (C) period.

Treatment

Starting on day 6, prednisolone (PrednisTab, Lloyd, Inc. of Iowa) was administered to each dog as 0.5 mg/kg *per os* every 12 hours, for a total daily dose of 1 mg/kg/day. Medication administration occurred in the morning at approximately 7am and in the evening at approximately 7pm. Daily water intake and USG were then measured as described for days 1-5. This was the prednisolone (P) treatment period.

Blood was collected via jugular venipuncture into red top tubes for measurement of serum sodium, starting on day 3 of prednisolone treatment and performed every 72 hours thereafter to ensure significant hyponatremia did not develop.

After 7 days of oral prednisolone therapy, desmopressin acetate (Sun Pharma, Cranbury, New Jersey) administration was started in 6 out of 7 dogs, at a dose of 5 mcg every 12 hours subcutaneously for 5 days. This was the prednisolone plus desmopressin treatment period (PD). During this time period, daily water intake as well as daily USG were measured as previously described.

After finishing the desmopressin treatment, daily prednisolone therapy was continued and daily water intake as well as daily USG were measured as previously prescribed for 5 additional days. This was the prednisolone after desmopressin treatment period (PAD).

Statistical methods

Descriptive and inferential statistics were performed using commercially available statistic software (SAS for Windows v. 9.4, SAS Institute, Inc. Cary, NC). For each dog, a mean urine specific gravity (USG) and mean water intake was calculated for each treatment period, using the values for the last three days of each treatment. Sodium concentration was measured once for each dog during each treatment period. The effect of treatment on the mean value of USG and water intake, and sodium concentration was assessed using a generalized linear mixed model within PROC MIXED. For each model, patient I.D. was considered a random variable. Inspection of conditional residuals was used to assess if model assumptions were met. The model of water intake did not meet the assumptions of homoscedasticity and normality of the residuals, so the data for outcome water intake was log 10 transformed. For each model, least square means were calculated for each level of treatment, and the following sequential comparisons among treatment levels were made: control (C) vs prednisolone (P), prednisolone (P) vs prednisolone plus desmopressin (PD), prednisolone plus desmopressin (PD) vs prednisolone after desmopressin (PAD), prednisolone (P) vs prednisolone after desmopressin (PAD), and control (C) vs prednisolone plus desmopressin (PD). The least squares means are presented in Table 1. Dog body weight at the beginning of the treatment period, compared to

body weight at the end of the treatment period, was evaluated using a paired sample t-test in PROC TTEST. An alpha level of 0.05 was used to determine statistical significance.

Results

Baseline characteristics of study subjects

Seven dogs were initially enrolled. All received prednisolone as described. Six of seven dogs received desmopressin injections as described. Desmopressin was withheld from one dog because this individual dog did not become polydipsic or polyuric during the prednisolone treatment period. Her 3 day mean water intake was 56 mL/kg/day, and her urine remained concentrated with a 3-day mean specific gravity of 1.033. Therefore, concern for development of significant free water overload and hyponatremia following administration of desmopressin precluded safe administration. Data from this dog was excluded from analysis of serum sodium levels.

Effect of treatment on USG and water intake

Administration of desmopressin significantly decreased and increased water intake and urine specific gravity. Treatment least squares means and their standard errors for each of the outcomes are presented in Table 1. Treatment was significantly associated with USG ($p<0.001$), $\log_{10}$ water intake ($p<0.001$), and sodium concentration ($p<0.001$). Sequential comparisons of least squares mean estimates of treatment levels were performed for each outcome. When compared to the previous treatment, each dog had a significant change in USG (Figure 3.1). In

the model of USG, treatment level comparisons of least square means were as follows: C vs P ($p=0.014$), P vs PD ($p<0.001$), PD vs PAD ($p<0.001$), P vs PAD ($p=0.479$), and C vs PD ($p=0.022$). In the model of logH2Oml/kg, treatment level comparisons of least square means were as follows: C vs P ($p<0.001$), P vs. PD ($p=0.007$), PD vs PAD ($p<0.001$), P vs PAD ($p=0.037$), and C vs PD ($p=0.702$) (Figure 3.2).

Effect of treatment on serum sodium concentrations

No significant difference was detected when sodium concentration prior to treatment (C) were compared to those following administration of prednisolone (P). There was a significant decrease in serum sodium after administration of desmopressin (PD) and a significant increase 36 hours after desmopressin administration was discontinued (PAD), while the dogs were still receiving prednisolone (Figure 3.3). In the model of sodium concentration, treatment level comparisons of least square means were as follows: C vs P ($p=0.985$), P vs. PD ($p=0.001$), PD vs PAD ($p<0.001$), P vs PAD ($p=0.405$), and C vs PD ($p=0.001$).

Effect of treatment on weight

Dog weight at the start of the treatment period (mean = 27.96, std. dev. = 5.85) was greater than dog weight (mean = 26.39, std. dev. = 5.79) at the end of the treatment period ($p<0.001$).

Discussion

Results of this study indicate that administration of desmopressin significantly decreased the polyuria and polydipsia exhibited by dogs during prednisolone administration. This supports the theorythat prednisolone causes polyuria and polydipsia by either inhibiting release of ADH, or antagonizing the action of ADH in the renal tubule.

There was a large amount of individual variation in both the polydipsia induced by prednisolone (P) and the improvement (decreased water consumption) in response to desmopressin (PD). Of the six dogs who were treated with desmopressin, the mean decrease in water consumption was 52.1 mL/kg/day (median: 32.5). This did vary widely, however, from 17.2 mL/kg/day to 177.3 mL/kg/day. Additionally, desmopressin was never administered to one of the seven dogs due to a lack of polyuria and polydipsia after prednisolone administration. This situation may represent the 10% of dogs with hyperadrenocorticism that are not polyuric or polydipsic (Perez-Alenza & Melian, 2017), despite these being considered the main clinical signs associated with the disease.

In all but one dog, the USG was higher in dogs treated with desmopressin when the control (C--no treatment) period was compared to the PD group, and the comparison of least square means showed a significant difference in C vs PD ($p=0.022$). There was also a significant decrease in Na concentration in the dogs receiving prednisolone when desmopressin was added as a treatment (P vs PD, $p=0.001$), and the least square means comparison of Na concentration between C and PD showed that there was a significant decrease in the PD group

(p=0.001). Additionally, the least square means of logH2Oml/kg was not different between C and PD (p=0.702). This means that, when compared to the control period, desmopressin administration normalized the increased water intake caused by prednisolone, and caused the urine to be concentrated excessively compared to control, causing free water retention and a decrease in Na concentration. This is likely due to the renal free water resorption caused by the desmopressin and unrestricted water intake in the dogs. This confirms that the polyuria and polydipsia caused by prednisone is due to inhibition of pituitary secretion or renal tubular action of ADH. A lower dose of desmopressin may have prevented or lessened the decrease in sodium.

The authors have heard (anecdotally) primary polydipsia as an explanation for the cause of PU/PD by prednisolone. Although water intake was not different between the C and PD groups, the Na concentration decreased. In normal dogs, the thirst response should decrease with hyponatremia (and subsequent hypoosmolality), but it did not, so primary polydipsia cannot be ruled out. However, in people treated with desmopressin with diabetes insipidus, hyponatremia is the most common complication. One explanation in people, which may also apply in dogs, is that fluid intake is social and habitual, rather than thirst driven, so fluid intake may be in excess of physiological needs, resulting in hyponatremia (Behan et al., 2015).

The magnitude of decrease in Na concentrations in some of the dogs in the PD group was clinically significant. Although the least square means Na concentration in the PD group was 136 mEq/L, one dog decreased from 142 mEq/L to 131 mEq/L. This decrease took place over a 3-day period. Acute decreases in Na can be detrimental, resulting in seizures and

cerebral edema (DiBartola, 2012). In severely hypernatremic dogs, it is recommended to decrease the Na concentration by no more than 0.5 to 1.0 mEq/L/hr) to prevent neurologic complications (Silverstein & Hopper, 2015). No clinical signs associated with the Na decrease were noted in any of the dogs in our study. Unfortunately, concurrent desmopressin and prednisolone therapy was only continued for 5 days, so it is difficult to know whether the Na concentrations would continue to decrease more over a longer period of time. Additionally, one dose of desmopressin (5 mcg/dog) was used for all dogs. A lower dose is likely to have resulted in less clinically significant hyponatremia, but this was not studied. Although water restriction would also lessen the severity of hyponatremia, this was not attempted, and is not recommended in clinical patients due to potential complications associated with over-restriction. In people with diabetes insipidus and hyponatremia associated with desmopressin use, one recommendation is to skip one dose of desmopressin per week to allow for aquaresis (Behan et al., 2015).

In this study, prednisolone was chosen as the glucocorticoid administered at a dosage of 1mg/kg/day, representing what many practitioners use as the high end of the anti-inflammatory dosage for prednisolone. Administration of higher prednisolone dosages would be expected to result in the same side effects but with increased magnitude. Desmopressin was administered subcutaneously rather than orally or conjunctivally to ensure consistent absorption, as the experience of two of the authors has been that patients with central diabetes insipidus that do not respond to ocular administration of desmopressin may respond to subcutaneous injections.

Our study had several limitations. Only one breed of dog, the Walker Hound, was utilized; other breeds may respond differently to prednisolone. However, significant variation was noted, even within this breed. Although urine collection was attempted around noon each day, it was not successful in each individual dog and urine samples obtained within a 6 hour window was used in the statistical analysis. Cystocentesis would have allowed more consistency regarding timing of urine collection, but was not pursued due to concerns posed by IACUC regarding daily cystocenteses.

Another weakness is that water intake was not measured after prednisolone was discontinued. Given that the water intake increased following discontinuation of desmopressin while the dogs were still on prednisolone, even though it wasn't a statistically significant increase, it would have been interesting to note if water intake decreased back to baseline values after discontinuation of prednisolone. Unfortunately, this data was not obtained, but should be considered for similar studies in the future.

This is the first study to document a decrease in water intake and increase in urine specific gravity when subcutaneous desmopressin was administered to dogs receiving prednisolone. Sodium concentration also decreased in these dogs. Future studies should include different routes of administration (conjunctival and/or oral) of desmopressin, and adjustment of desmopressin dose based on sodium concentration.

Table 3.1 Treatment least squares means ± standard errors for urine specific gravity, log10 water intake, and sodium concentration.

Treatment	Urine Specific Gravity	Log_{10} Water Intake (ml/kg)	Sodium (mEq/L)
Control	1.034 ± 0.0038	1.59 ± 0.058	143.4 ± 1.13
Prednisone	1.020 ± 0.0038	1.93 ± 0.058	142.9 ± 1.13
Prednisone plus Desmopressin	1.047 ± 0.004	1.67 ± 0.062	136.2 ± 1.13
Prednisone after Desmopressin	1.015 ± 0.004	2.14 ± 0.062	145.2 ± 1.13

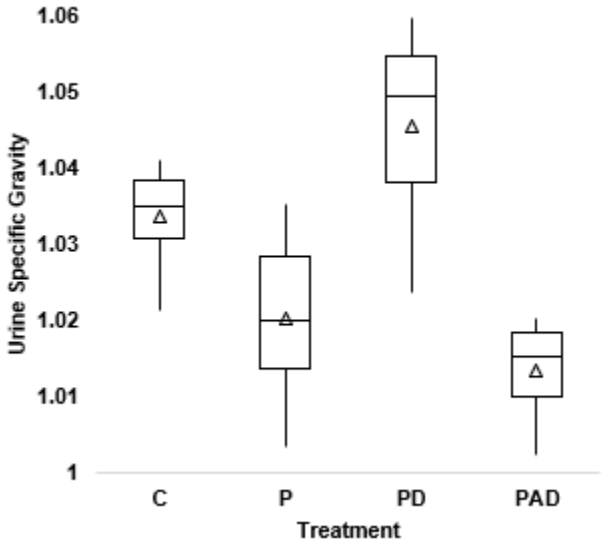

Figure 3.1 Box and whisker plot displaying descriptive statistics for urine specific gravity (USG) for the means of dogs during each phase of treatment. Plot displays minimum, 1st quartile, median, mean (Δ), 3rd quartile, and maximum values.

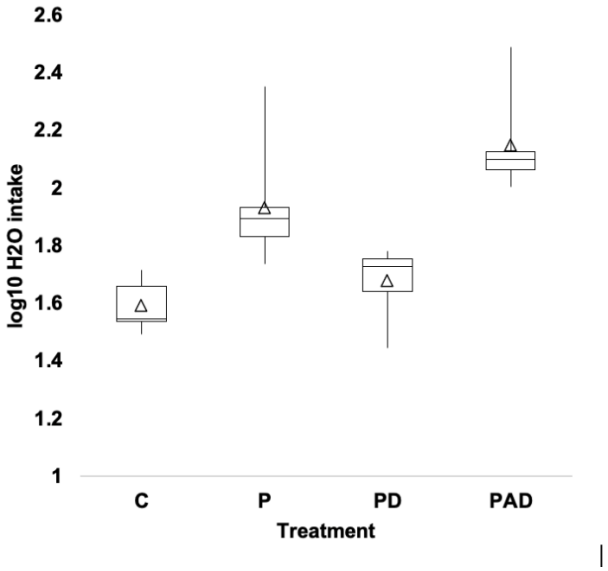

Figure 3.2 Box and whisker plot displaying descriptive statistics for log10 H2O intake for dogs during each phase of treatment. Plot displays minimum, 1st quartile, median, mean (Δ), 3rd quartile, and maximum values.

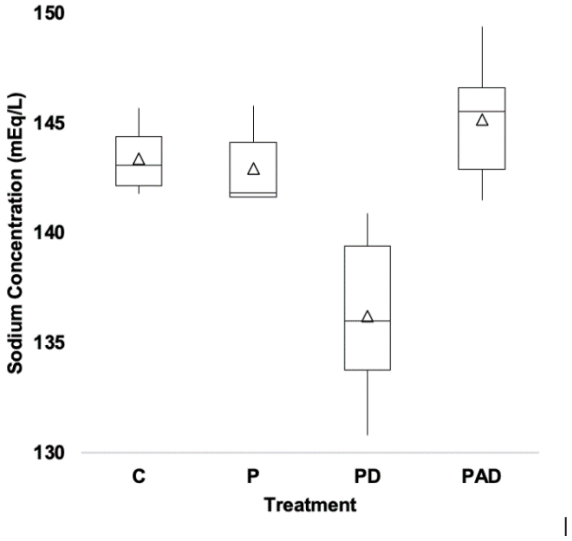

Figure 3.3 Box and whisker plot displaying descriptive statistics of blood sodium concentration during each phase of treatment. Plot displays minimum, 1st quartile, median, mean (Δ), 3rd quartile, and maximum values.

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CHAPTER IV

CONCLUSION

The results of the research investigation discussed in this thesis revealed that the subcutaneous administration of desmopressin acetate at a dose of 5mcg per patient was effective in reducing water intake and increasing urine specific gravity in a small group of dogs that were also administered prednisolone at an anti-inflammatory dose. Subcutaneous administration of desmopressin appeared well-tolerated in the dogs in this study. Twenty-five gauge needles were used, and the small needle gauge likely contributed to patient comfort. It would be reasonable to dispense U-100 insulin syringes to owners to ensure adequate dosing. A tutorial in injection administration could be performed similar to that utilized for owners of diabetic pets.

Concessions such as these will likely enable owners to manage the most common side effects of prednisone and prednisolone, namely polyuria, polydipsia (PU/PD), and polyphagia, while maintaining dogs on glucocorticoid doses that are appropriate for the underlying disease process. It has been our clinical experience that owners will sometimes discontinue glucocorticoids due to excessive PU/PD, without first consulting the clinician, and the cessation of steroids has resulted in exacerbation of the underlying condition, and even death. If the

owner is aware that there is a simple way to decrease the degree of PU/PD whilst maintaining the beneficial effects of glucocorticoids, these situations may be prevented in the future.

Other options that may decrease PU/PD include use of dexamethasone or methylprednisolone, due to reduced mineralocorticoid activity in comparison to prednisone or prednisolone (Reusch, 2015). Methylprednisolone is however considerably more expensive than prednisone or prednisolone, and dexamethasone may be more ulcerogenic. As glucocorticoids are considered superior to other immunosuppressives in rapidity of onset of action, and sometimes in efficacy, the ability to use prednisolone could improve chances of remission and/or reduce reliance on other immunosuppressive drugs such as modified cyclosporine, azathioprine, mycophenolate, and leflunomide. In some cases, the cost of the aforementioned medications or the required monitoring makes their use problematic for owners.

In contrast, desmopressin is relatively affordable and available in multiple formulations, including oral tablets, nasal sprays, and solutions for injection. Any of these can be obtained from a local human pharmacy, or from a compounding pharmacy. The intranasal preparation of desmopressin acetate, in particular, is considered safe for subcutaneous administration after it's placed in a sterile multi-use vial after being filtered through a bacteriostatic filter(Mansell & Parry, 1991; Nichols, 2000), and a 90-day supply can be purchased for approximately $50-100 with the use of pharmacy discount programs. These forms of desmopressin can also be purchased through compounding pharmacies such as Wedgewood Veterinary Pharmacy. On the Wedgewood site, the cost of solutions for injection is markedly lower than commercially

available injectable (ie. 5mL of 0.01% solution for $58) DDAVP, but similar to the cost of the intranasal solution available commercially which is suitable for subcutaneous administration. The compounding pharmacy also has oral liquids available for pets whom may not tolerate tablets, injections, or eye drops. Of course, additional studies using these various formulations would be necessary to ensure the results are similar to those obtained with commercially available formulations.

The most significant drawback to using desmopressin is the potential to cause hyponatremia. Because there was significant drop in serum sodium during desmopressin administration in our study, use in clinical patients would require frequent monitoring of electrolytes. This may represent a hinderance to some owners. It is likely, however, that once a dose is administered for a certain period of time, the frequency of bloodwork to monitor electrolytes could be decreased. Further studies to explore this are indicated in order to guide clinicians in their decision-making.

Similar to desoxycorticosterone pivalate use for mineralocorticoid supplementation in hypoadrenocorticism, desmopressin dose titration “to effect” may be possible. This could mitigate the potential side effects of hyponatremia. Additional studies with varying doses of desmopressin would provide helpful clinical insight and guidance.

There is a vast potential for further study in this field. Subcutaneous administration of DDAVP was used due to perceived improved absorption versus ocular or oral administration. Ocular and oral administration would undoubtedly be easier for owners. Thus, future studies

should evaluate these routes. Although DDAVP would be expected to have similar effects when used with different glucocorticoids, this is another potential are of study. Lastly, this study was performed in laboratory dogs under controlled conditions. The most clinically relevant follow-up study would evaluate the use of desmopressin in clinical patients receiving prednisolone or other glucocorticoids for glucocorticoid-responsive conditions.

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