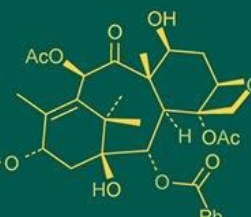
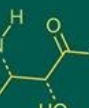
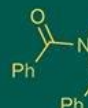


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Case report: Efficacy of combine therapy of betahistine dihydrochloride & pentoxifyllin in the treatment of peripheral vestibular syndrome in dog

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Abstract

Geriatric canine vestibular illness/idiopathic vestibular syndrome, sometimes referred to as old dog vestibular sickness, is the most common cause of acute unilateral peripheral vestibular dysfunction in older dogs. The disease is characterized by ataxia with a horizontal or rotatory nystagmus, head tilt, and loss of balance. The majority of experts characterized IVS as a peripheral vestibular illness that can affect cats of any age and elderly canines and is acute to peracute, improving, and non-painful. Assessing the effectiveness of pentoxifylline and betahistine HCL combination therapy in the treatment of canine idiopathic/geriatric vestibular illness was the aim of the study and case report. A 12-year-old dog, sex-male, breed-Mongrel, weighing 18 kg was presented to, PetVet clinic, kalyan-421301 with complaint of imbalance while waking, one side head-tilt, occasional vomiting and pruritic in left ear in the last 6 days. With the help of diagnostic aids available as well as differentiating presented clinical signs as against other differentials, the presented case was diagnosed as, geriatric canine vestibular illness/idiopathic vestibular syndrome. Along with fluid therapy and anti-emetics, this study used novel approach with usage of combination therapy of pentoxifylline and Betahistine Hcl for the treatment. Within 5 days of initiation of therapy dog started to balance its body with normal gait. There was absence of head tilting towards any ear and vomiting was also reduced considerably and other associated symptoms were also decimated with complete recovery in affected dog in 12 days. No reoccurrence of signs were observed.

Keywords: Betahistine Hcl, Idiopathic vestibular syndrome, old dog vestibular disease, pentoxifylline

Introduction

The part of the neurological system in charge of preserving balance and equilibrium is called the vestibular system (VS) (Kent *et al*, 2010; Rossmesl, 2010) ^[1, 2]. The sensory system called vestibular is in charge of preserving posture, balance, and tone of the head and body in response to movement and gravitational forces. The vestibular part of the vestibulocochlear nerve (cranial nerve [CN] VIII) and the membranous labyrinth are components of the peripheral vestibular system, which primarily exists in the petrosal region of the temporal bone. Receptors of peripheral vestibular system located in inner ear and the central vestibular system, positioned inside the brain, receives signals acquired by the peripheral vestibular system (Ettinger & Feldman, 2017) ^[4]. The most frequent cause of acute unilateral peripheral vestibular dysfunction in elderly dogs is geriatric canine vestibular illness/idiopathic vestibular syndrome, also known as old dog vestibular disease. This idiopathic sickness typically manifests at a mean age of 12.5 years. Head tilt, loss of balance, and ataxia with a horizontal or rotatory nystagmus are the disorder's hallmarks. These symptoms appear quite suddenly (Nelson & Couto, 2019) ^[3]. Otitis media and interna, canine hypothyroidism, infections, neuritis, vascular insults, trauma, and neoplasia are significant differential diagnoses for peripheral causes (Radulescu,2020) ^[12].

Line of treatment against geriatric vestibular disease includes, Antiemetics and fluid therapy as well as drugs causing vasodilation resulting in increasing blood flow towards peripheral organs such as ear. Fluid therapy might be necessary if the patient is vomiting and/or dehydrated e.g. Meclizine (12.5 to 25 mg per pet PO q 24 h) has antiemetics and antivertigo properties. The current case describes, peripheral-geriatric vestibular disease in mongrel dog and efficacy of combination therapy of pentoxifylline and Betahistine dihydrochloride.

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Case History and observation

A 12-year-old dog, sex-male, breed-Mongrel, weighing 18 kg (Fig 1) was presented to, PetVet clinic, kalyan-421301 with complaint of imbalance while waking, one side head-tilt, occasional vomiting and pruritic in left ear in the last 6 days. The appetite, food and water intake of dog was reduced. The animal was active and alert to surrounding at the time of presentation. The body temperature was 101.5 °F, mucous membrane was slight pale, normal sized lymph node and in auscultation there were no abnormal lung sounds. The deworming and vaccination were infrequent in dog. On careful examination of left side ear revealed discomfort to dog, for further examination dog was properly restrained and with help of ear cleanser and cotton, ear was cleaned internally. This procedure revealed presence of blood tinges on cotton, possible acute internal ear infection. Horizontal nystagmus was observed in the animal when ocular examination carried out. The other neurological examination parameters such as, the mental status, proprioception, spinal reflexes and deep pain sensation testing, pedal reflex, corneal reflex were normal. Peripheral vestibular signs with or without facial nerve paralysis have also been seen in hypothyroid-associated polyneuropathy in dogs, so to exclude hypothyroidism induced peripheral vestibular disease, the blood sample were drawn for CBC, LFT, KFT and thyroid tests analysis, reports in (Table 1). As per haemato-biochemical estimation all the values were in normal range including that of total T4, which in turned excluded hypothyroidism induced peripheral vestibular disease w.r.t this case. In central vestibular disease, parameters such as bidirectional head tilt, loss of consciousness, changing Direction with head position are evident, none of them were present while examining the dog as a reason symptomatically central vestibular disease was excluded from diagnosis. Following a thorough neurological examination, the following deficiencies were noted: a left-sided head tilt, a wide base stance on both thoracic and pelvic limbs, horizontal nystagmus, a slight decrease in left-sided facial sensitivity, vestibular ataxia marked by imbalance, a persistent propensity to look for wall support in order to maintain the patofodial position, and successive falls on the left side (Figure 1). Test results for deep pain perception, proprioception, spinal reflexes, and mental state were all normal. As a result, the damage mainly occurred to the left vestibular apparatus.



Fig 1: A 12-year-old dog, sex-male, breed-Mongrel, weighing 18 kg (Before Therapy)

Test	Unit	Result
Haemoglobin	g %	9.5
RBC count	Million/cu.mm	5.5
Total WBC count	/cumm	8000
Platelet count	×1000/ cumm	175
Blood Urea Nitrogen	mg/dl	23.3
Creatinine	mg/dl	1.9
Alkaline Phosphatase	IU/L	101.4
Bilirubin Total	mg/dl	0.2
Bilirubin Direct	mg/dl	0.1
Bilirubin Indirect	mg/dl	0.1
S.G.O. T	IU/L	48.8
S.G.P. T	IU/L	54.3
Total Proteins	gm/dl	5.9
Albumin	gm/dl	3.0
Globulin	gm/dl	2.9
Total T4	nmol/l	20

Treatment

- The clinical management of geriatric vestibular disease was initiated with, flushing of left ear canal with Tris-EDTA ear cleanser. The owner was advised to clean affected ear weekly once.

Alkalinizing solution, antibiotic potentiating agent, and antibacterial flush are the three main purposes of Tris-EDTA. When gram-negative bacteria are exposed to EDTA, their cell surfaces are degraded. EDTA's impact is amplified by Tris buffer. By soaking the ear canal in an EDTA-tris solution, bacterial cell walls may be damaged.

- An anti-vertigo drug - Tab. Betahistine Hcl @ 0.2 mg/kg B.I.D for 12 days.

As an agonist of the histamine H1 receptor and antagonist of the histamine H3 receptor, it reduces activation of the vestibular nuclei and increases cerebral blood flow through vasodilation. This mechanism is believed to improve central compensation for vertigo

- Tab. Pentoxifylline @15mg/kg P.O. B.I.D for 12 days
Pentoxifylline is an unspecific PDE inhibitor, the rationale behind the present study was that pentoxifylline-induced inhibition of PDE1C2 could result in increased intracellular concentration of cAMP. This elevated cAMP level could lead to increased response of olfactory sensory neurons to chemical stimuli, which in turn could have an effect on human olfactory sensitivity (Gudziol and Hummel, 2009) [8]. Pentoxifylline increases red blood cell flexibility by increasing erythrocyte ATP and cyclic nucleotide levels. It reduces the viscosity of blood by decreasing erythrocyte aggregation and stimulating fibrinolysis to reduce plasma fibrinogen concentrations. All these effects enhance the ability of blood to flow through peripheral vessels (hemorheological action) (<https://www.ncbi.nlm.nih.gov/books/NBK559096/>) [9].

- Tab. Ondansetron @1mg/kg P.O. B.I.D for 12 days

Utilized as anti-emetic to counter vomiting in patient. Mentioned therapeutic approach was followed for clinical management of geriatric vestibular disease in animal. Within 5 days of initiation of therapy dog started to balance its body with normal gait. There was absence of head tilting towards any ear and vomiting was also reduced

considerably. With weekly flushing and cleaning of left ear, the pruritic sight was totally absent. The appetite of the dog improved gradually. Nystagmus as one of observation at the time of presentation, was completely subsided after therapy and there has been no recurrence of neurological signs in the dog (Fig 2).



Fig 2: A 12-year-old dog, sex-male, breed-Mongrel, weighing 18 kg (After Therapy)

Discussion

Idiopathic Vestibular Syndrome has been the subject of an increasing amount of research in recent years. Several writers have proposed renaming IVS as facial and vestibular neuropathy of unknown origin (FVNUO) or benign peripheral vestibular syndrome (Orlandi *et al.*, 2020) [10]. The objective behind the study and case report was to access the efficacy of combination therapy of pentoxifylline and betahistine Hcl in treatment of canine idiopathic/ geriatric vestibular disease. The definition of IVS is vague, and diagnostic and treatment methods have not been widely modified in spite of these developments. A vestibular lesion will result in an imbalance where the normal side pushes the head and body toward the abnormal side. This is because the extensor muscles on one side are not as well-facilitated. Head tilt to one side and lack of balance are common symptoms of unilateral or asymmetric illness processes. Research revealed that the primary distinction between IVS and other vestibular system disorders in dogs and cats is that the former do not exhibit Horner's syndrome and do improve (Harrison *et al.*, 2021) [11]. Higher age, body weight, pathological nystagmus, facial nerve paresis, and a peripheral neuroanatomical localization were further risk factors identified in the statistical model for dogs. Achieving the same degree of specificity in the localization of vestibular disorders as is observed in human medicine is made more difficult by the impracticality of some diagnostic techniques in veterinary settings as well as the inherent constraints of treating animals as patients. However, these issues are still being addressed and vestibular disease diagnostic capacities are being improved by continuing research and developments in veterinary neurology.

Bilateral engagement is may present. Nucleus tractus solitarius, the dorsolateral reticular formation of the caudal medulla (lateral tegmental field), and the parabrachial nucleus play key roles in integrating signals that trigger nausea and vomiting (Yates *et al.*, 2014) [5]. In peripheral vestibular disease, the pathologic nystagmus can be

horizontal or rotary and the fast phase is always away from the lesion (Ettinger and Feldman, 2017) [4]. Symptoms like head tilt, vestibular ataxia with leaning, pathological nystagmus or strabismus should guide the examiner to diagnose a lesion of the vestibular system (Turbatu *et al.*, 2019) [6]. Maropitant (1 mg/kg SC q 24 h or 2-8 mg/kg PO q 24 h in dogs and 1 mg/kg PO q 24 h in cats) is a neurokinin-1 inhibitor, which blocks the action of substance P to the final common pathway in the emetic center in the brain.

A substance called betahistine dihydrochloride shares structural and pharmacological characteristics with histamine, but it has a longer central vasodilation impact and less of an effect on increasing stomach output.

Numerous investigations have demonstrated the potent cerebral vasodilator properties of betahistine. It is more effective in increasing blood flow from the vertebro-basilar artery system, which irrigates the posterior brain and improves internal vestibular and auditory system microcirculation (Turbatu *et al.*, 2019) [6]. Pentoxifylline is in the same class as caffeine, has anti-inflammatory properties. It helps to decrease clot formation, improve circulation, and enhance wound healing. There is a fairly broad dosing range for pentoxifylline: typically, 10-30 mg/kg twice a day to three times a day (Kennis, 2022) [7].

Conclusion

Idiopathic vestibular disease (IVS), is neurological disorder frequently occurring in geriatric dogs as well as cats with ear infections/inflammations. The presented case after complete and thorough examination was diagnosed as vestibular disease and managed with novel approach with combination therapy of pentoxifylline as well as Betahistine Hcl. The results of this approach encouraging results and usage of this combination therapy can me further enhanced.

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