Hyoscyamine Sulfate for the Treatment of Clinical Bradycardia in Two Dogs and One Cat

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ABSTRACT

The objective of the case series is to describe the use of hyoscyamine sulfate for clinical bradycardia in dogs and cats. Two dogs and one cat presented for clinical atrioventricular block. For various reasons, pacemaker implantation was not performed. Therefore, conservative management with hyoscyamine sulfate was initiated and resulted in resolution of clinical signs without any reported side effects. To the best of the authors' knowledge, this is the first case series describing the use of hyoscyamine sulfate in the treatment of bradycardia in dogs and cats. For clinical bradycardia in which pacemaker implantation is not possible, oral hyoscyamine sulfate therapy should be considered.

Keywords: Anticholinergics; Atrioventricular Heart Block; Syncope.

CASE DESCRIPTION

Case 1: A 13-year-old intact male German shepherd was referred for evaluation of a 2-week history of coughing, exercise intolerance, and syncope with no identifiable "trigger". The syncopal episodes were characterized by: loss of consciousness, could occur with minimal activity or during transition from less to more activity, no urination/defecation, flaccid paralysis, pale mucous membranes, a duration of approximately 1 minute, and recovery was quick (approximately 1 minute). According to the owner, 3-4 syncopal events would occur daily. There was no other significant medical history reported.

Salient features on physical examination were a heart rate of 72 bpm with a regular rhythm, a grade III/VI left apical systolic heart murmur, panting, and normal synchronous pulses.

Static electrocardiogram (ECG) revealed a heart rate of 60 bpm. The rhythm was regular with no identifiable P-waves and an accelerated ventricular rhythm. Given the absence of P-waves and ventricular rhythm, the ECG diagnosis was atrial fibrillation, atrioventricular (AV) block and an accelerated ventricular rhythm (Figure 1). Additional diagnostics consisted of a complete blood count, serum chemistries, urinalysis, thoracic radiographs, abdominal radiographs, abdominal ultrasound, an echocardiogram and an atropine response test. The complete blood count, serum chemistries, urinalysis, abdominal radiographs and abdominal ultrasound were unremarkable. Thoracic radiographs revealed left-sided cardiomegaly with normal pulmonary vasculature and parenchyma.

On subjective 2-D echocardiographic evaluation (Vivid q, GE Health Care, Wauwatosa, WI), no effusions or spontaneous echocardiographic contrasts were noted. The left atrium appeared moderately dilated. The mitral valve leaflets appeared mildly degenerative. Left ventricular chamber size appeared normal. The interventricular septum and left ventricular free wall appeared normal in thickness. Left ventricular wall motion appeared normal. All other

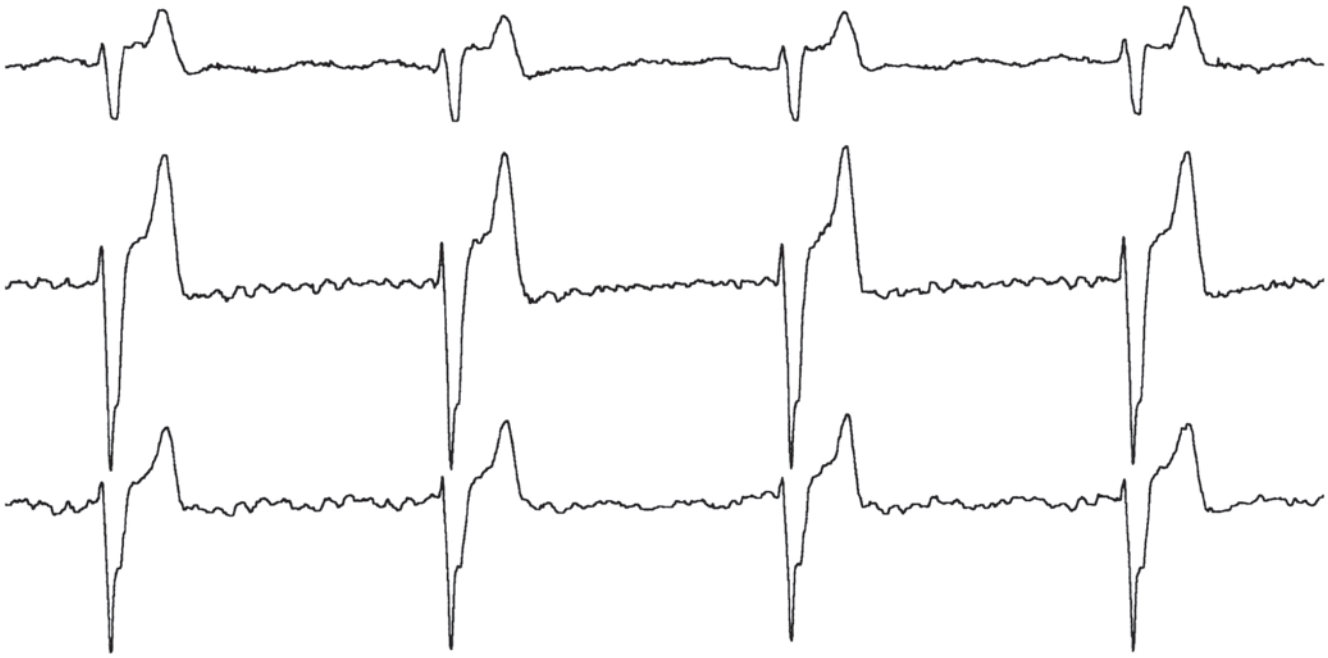

Figure 1: Static ECG from a 13-year-old German Shepherd presented for syncope; Leads 1, 2, and 3 (top to bottom respectively), paper speed 50mm/s, amplitude 10mm/mV; The ECG is consistent with atrial fibrillation and heart block.

cardiac structures appeared subjectively normal. Color-flow Doppler (Vivid q, GE Health Care, Wauwatosa, WI) evaluation revealed moderate mitral regurgitation, trivial tricuspid regurgitation, laminar flow within the left ventricular outflow tract, and laminar flow within the right ventricular outflow tract.

In summary, the echocardiographic examination was consistent with stage B2 myxomatous valvular disease with moderate left atrial dilation and no evidence of structural heart disease to account for the AV block (1). An atropine response test revealed a heart rate of 100bpm (Figure 2). The rhythm was regular with no identifiable P-waves and an accelerated ventricular rhythm. The atropine response test was consistent with atrial fibrillation with heart block and an accelerated ventricular rhythm. The post-atropine ventricular rate was faster compared to baseline.

Given the heart block and syncope, pacemaker implantation was recommended but declined by the owner. Given the partial response to atropine, extended release hyoscyamine sulfate (0.01mg/kg PO every 12 hours) (Levbid, Acella Pharmaceuticals, Alpharetta, Ga) was prescribed. The patient's syncopal episodes resolved, the owner reported an improvement in exercise intolerance/activity and side effects were not reported. Due to the development of pre-syncopal episodes approximately 5 months following diagnosis, theophylline (10mg/kg PO every 12 hours) (Theophylline Quad Tab, Wedgewood Pharmacy, Swedesboro, NJ) was added to the treatment regimen. The owners elected euthanasia approximately 2-years following the initial diagnosis due to progressive paraparesis/paralysis of unknown etiology. Necropsy was not available.

Case 2: A 12-year-old FS Bichon Frise presented for repeated episodes of collapse over 2 weeks unresponsive to phenobarbital. The episodes were described as collapse of the pelvic limbs followed quickly by complete recumbency/unresponsiveness and quick recovery. She had a history of hyperadrenocorticism and was being managed with trilostane (1.5mg/kg PO every 12 hours) (Vetoryl, Dechra, Overland Park, KS).

Physical examination revealed a grade II/VI systolic murmur at the left apex, a heart rate of 100bpm with a regularly irregular rhythm and excessive body habitus (body condition score=4/5). The remaining physical examination

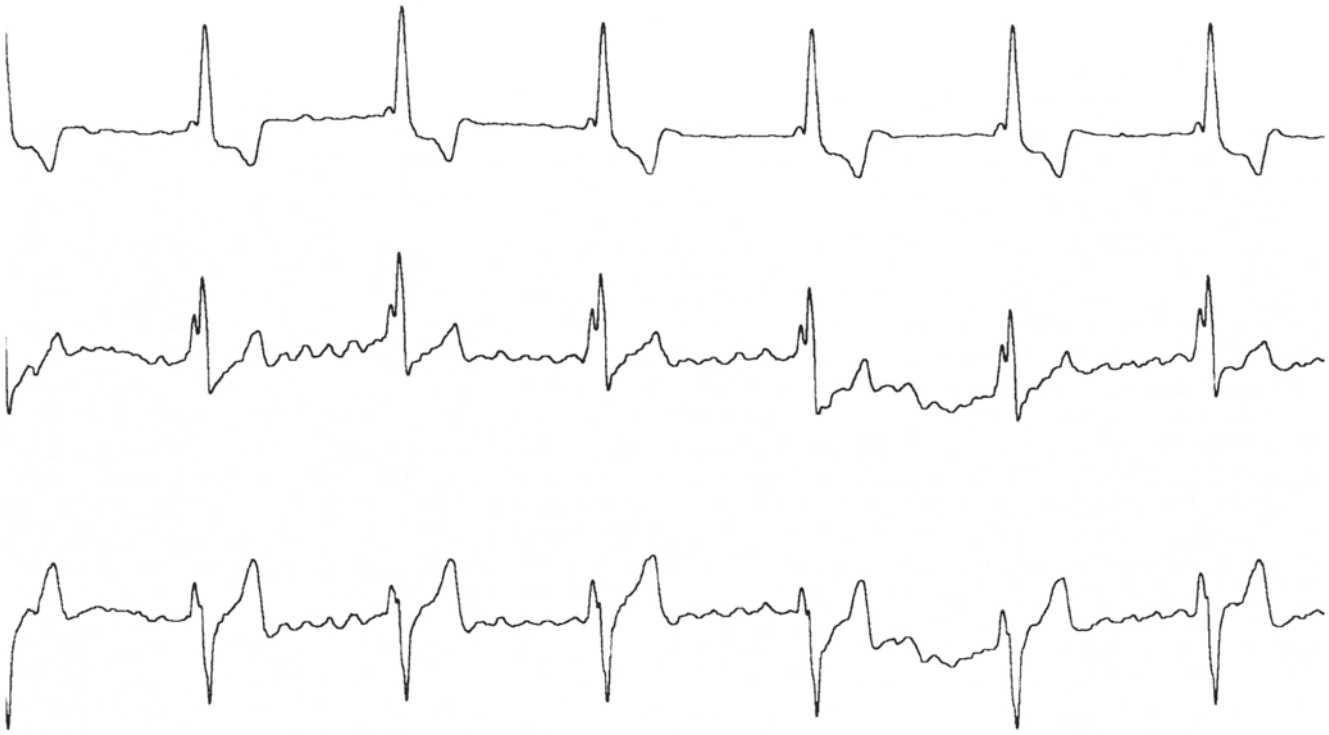

Figure 2: Atropine response test from a 13-year-old German shepherd presented for syncope. Leads 1, 2, and 3 (top to bottom respectively), paper speed 50mm/s, amplitude 10mm/mV The ECG is consistent with atrial fibrillation and heart block. Compared to baseline ECG, the heart rate is faster.

was unremarkable. Complete blood count, serum chemistries, and an ACTH stimulation test performed by the referring veterinarian were unremarkable.

Initial diagnostics consisted of a Doppler systolic blood pressure (Ultrasonic Doppler Flow Detector, Parks Medical, Aloha, OR) and an electrocardiogram (Eli 280, Mortara Instruments, Milwaukee, WI). The systolic blood pressure was determined to be 130 mmHg. The static ECG revealed a heart rate of 90 bpm. The ECG diagnosis was consistent with sinus arrhythmia. Given the absence of metabolic disease and the lack of response to phenobarbital, a 24-hour Holter monitor was recommended. The Holter monitor revealed a sinus arrhythmia with frequent intermittent high-grade (3:1 conduction) second-degree AV block (Figure 3). The maximum (1 minute average), mean, and minimum (1 minute average) heart rates were 144, 76, and 46 bpm. The longest R-R interval was 3.43 seconds at 10:26 am. Given the high-grade second degree AV block, hyoscyamine sulfate elixir (Levsin, Silarx Pharmaceuticals, Carmel, NY) therapy was initiated (0.005mg/kg PO twice daily 8 hours apart). Repeat Holter monitor after initiating therapy was consistent with sinus arrhythmia and second-degree AV block (intermittent low grade second-degree AV block). The maximum (1 minute average), mean, and minimum (1 minute average) heart rates were 162, 92, and 65 bpm. The longest R-R interval was 2.6 seconds at 1:42 am. After initiating therapy approximately 2 years previously (there were no additional treatment modifications), collapse episodes have not been observed, the owner reported normal activity, and there were no reported side effects.

Case 3: A 15-year-old female spayed, Domestic Short Hair cat presented with a history of lethargy, weakness and hiding in unusual places. The cat had a 3-year history of chronic kidney disease and systemic hypertension. The systemic hypertension was initially being managed with enalapril (0.5mg/kg PO every 12 hours) (Vasotec, Wockhardt, Parsippany, NJ). Due to worsening of the systemic hypertension and azotemia, enalapril was discontinued and atenolol (6.25mg PO q 24 hours) (Tenormin, Teva Pharmaceutical Industries,

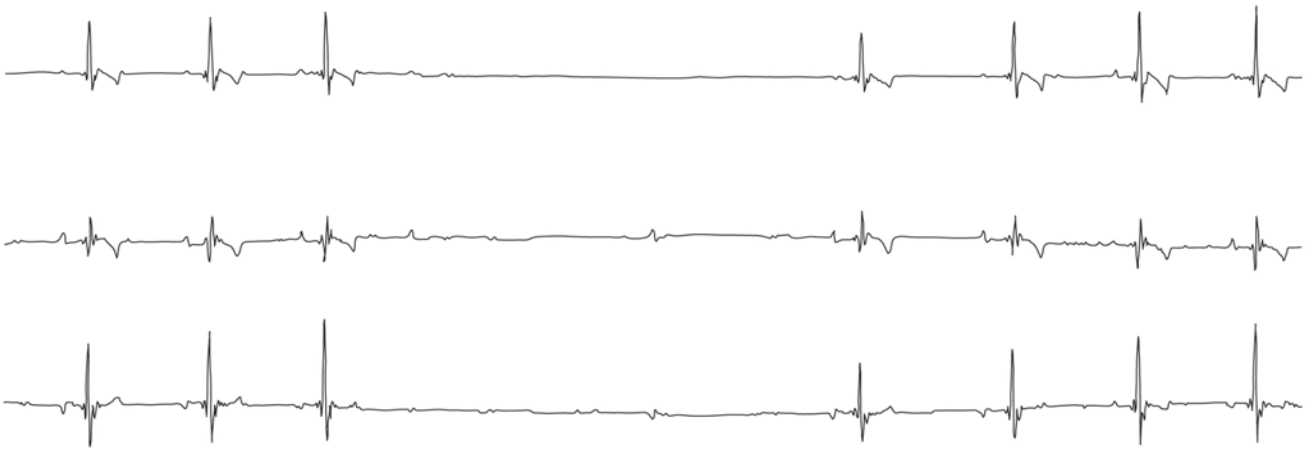

Figure 3. Holter strip from a 13-year-old Bichon Frise presented for syncope. The rhythm is consistent with sinus rhythm and advanced 2nd degree AV block (3:1).

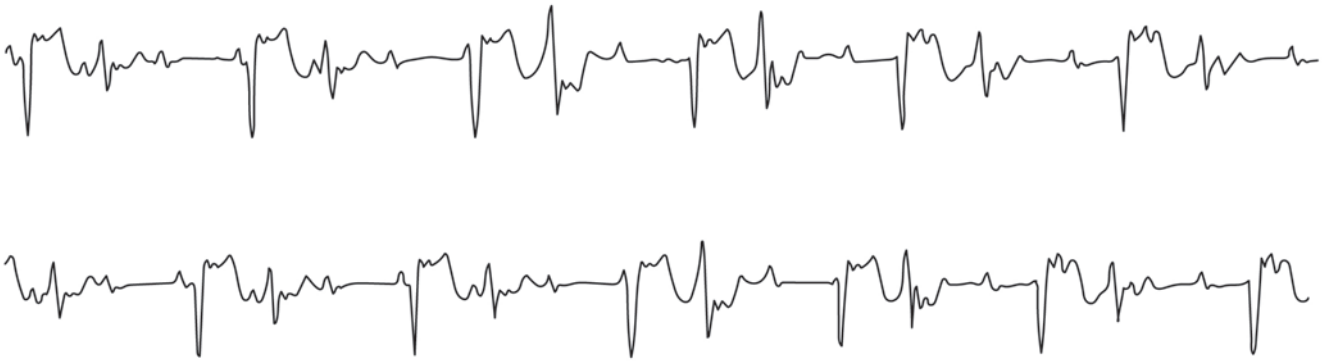

Figure 4. Static ECG from a 15-year-old DSH presented for lethargy and weakness. Lead 2, paper speed 25mm/s, amplitude 10mm/mV. The ECG is consistent with complete heart block with reciprocal beats or VPCs.

Parsippany, NJ) was added to the treatment regimen. About 15 months after initiating the atenolol therapy, syncopal episodes were noted. At that time, the atenolol therapy was discontinued and the syncopal episodes resolved. The systemic hypertension was managed with amlodipine (Norvasc, Alkem Laboratories, Fenton, MO) therapy.

Physical examination revealed an irregular rhythm and a heart rate of 120bpm. Complete laboratory data was consistent with stable kidney disease [BUN=25mg/dl (reference range=8-29mg/dl); creatinine=2.7mg/dl (reference range=0.6-1.4)]. Static ECG revealed a complete heart block with reciprocal beats or ventricular premature complexes (Figure 4). Hyoscyamine sulfate elixir (0.005mg/kg PO twice daily 8 hours apart) (Levsin, Silarx Pharmaceuticals, Carmel, NY) was prescribed. Since initiating therapy 4 months ago (there were no additional treatment modifications), the lethargy, weakness, and hiding in unusual places have resolved and side effects have not been reported.

DISCUSSION

Atrioventricular (AV) heart blocks is a rhythm disturbance that has been identified in dogs and cats (2-9). Atrioventricular blocks can occur at any age, but are more common in middle aged to geriatric dogs, geriatric cats, and cats with cardiomyopathy. Breeds of dogs more likely to develop heart block include Cocker spaniel, miniature

Schnauzer, Chow, English Bulldog and other brachycephalic breeds (2). The etiology of AV blocks is usually not apparent (4). In older patients, idiopathic fibrosis affecting the conducting system is often present (5). This fibrosis may be age related but may also be the result of ischemia from reduced cardiac blood supply. Minor, asymptomatic AV block is often related to hypervagatonia (4). Drugs that contribute to hypervagatonia (such as phenothiazine tranquilizers, narcotics, alpha-2 agonists) and drugs that block conduction through the AV node (such as beta-blockers and calcium channel blockers) can cause AV block (4).

The clinical signs associated with AV block often relate to bradycardia (5). Common signs reported are rear limb ataxia, rear limb paresis, lethargy, episodic weakness and syncope (5).

The diagnosis of AV block can be suspected on physical examination. Either a slow regular rhythm or a slow irregular rhythm will be noted on cardiac auscultation during persistent high-grade AV block. The static ECG will confirm AV block. In some patients, AV block may be intermittent and will not be noted on static ECG. In these cases, ambulatory ECG (Holter monitor, event monitor, implantable loop recorder, chest press ECG) will be required for definitive diagnosis.

Treatment is recommended for 2:1 second degree AV block associated with clinical symptoms, high-grade second degree AV block (3:1 or greater), and complete AV block (3,5). Given that the symptomatic bradycardia is considered life threatening, pacemaker implantation is the treatment of choice (2,3,5). However, experience has revealed that some patients in need never receive a pacemaker (8). This fact could be related to cost, geographic location, patient age, owner/clinician opinions/decision making, and/or possible comorbid disorders. If pacemaker implantation is not possible, then chronic oral antibradycardia treatment is the next best option. Oral antibradycardia treatments commonly recommended in veterinary patients are: beta-agonists (albuterol, terbutaline), phosphodiesterase inhibitors (theophylline, aminophylline or cilostazol), and anticholinergics (propantheline bromide, aminopentamide, and hyoscyamine sulfate) (6,8). There is sparse data in the literature on the utility and side effects of oral antibradycardia treatments. However, most reports indicate a lack of efficacy and discourage use due to lack of survival benefit (7,8). Oral antibradycardia therapy could be an appropriate alternative to alleviate symptoms related to bradycardia in cats in which pacemaker implantation may not impact survival (9).

This manuscript provides data on the use of hyoscyamine sulfate in the clinical treatment of bradycardia in 2 dogs and 1 cat. Hyoscyamine is a plant alkaloid found in the plant *Atropa belladonna*, or deadly nightshade, and in *Datura stramonium*, also known as jimsonweed (10). Hyoscyamine is the naturally occurring l-enantiomer, whereas atropine is racemic d,l-hyoscyamine (10). Both atropine and hyoscyamine block muscarinic receptors located in the heart and the gut (10). In people, hyoscyamine is commonly used to counteract the gastrointestinal side effects of cholinesterase inhibitors given to patients with myasthenia gravis (10). In addition, hyoscyamine has abolished episodes of high grade AV block associated with cholinesterase inhibitors in people (10). Although not commonly used in veterinary medicine, hyoscyamine may be useful for the treatment of bradycardia and hypermotile gastrointestinal conditions. Little is known regarding safety and efficacy in animals. Hyoscyamine sulfate elixir (0.125mg/5ml), drops (0.125mg/ml), tablets (0.125mg) or extended release tablets (0.375mg) are convenient products. For small dogs and cats (as in cases 2 and 3 above, the elixir and drops can be given at 0.005mg/kg PO every 8 hours. For owner convenience, we elected to administer the elixir twice daily (8 hours apart) due to the presumed absence of needed chronotropic support in the evening hours while sleeping. For larger dogs (as in case 1 above), the extended release tablets can be given at 0.01mg/kg PO every 12 hours. Dosage titration to effect without unacceptable adverse effects can be attempted. Typical adverse effects reported are mydriasis, mucous membrane dryness, lethargy, anorexia, urinary retention and gastrointestinal upset (11). Given the differing mechanism of action, hyoscyamine should be synergetic with beta-agonists and/or phosphodiesterase inhibitors. Theophylline was added to case 1 above for relapse syncope. Future pharmacokinetic and pharmacodynamic investigations, with a specifically determined physiologic response variable of interest, are required to best determine appropriate dosing.

In summary, hyoscyamine sulfate can be considered for the treatment of clinical bradycardia in dogs and cats in which pacemaker implantation is not possible. Hyoscyamine sulfate therapy can be dosed conveniently and safely with long term response possible.

Conflict of Interest: The authors declare no conflict of interests.

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