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Retrospective Evaluation of Sildenafil Citrate as a Therapy for Pulmonary Hypertension in Dogs

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Pulmonary arterial hypertension (PH) is a pathologic condition in dogs characterized by abnormally high pressures in the pulmonary circulation and has been associated with a poor outcome. Sildenafil is a type V phosphodiesterase inhibitor that produces nitric oxide–mediated vasodilatation. Sildenafil treatment decreases pulmonary arterial pressure and pulmonary vascular resistance in people with PH. The purpose of this study was to describe the clinical characteristics and outcome of dogs with PH treated with sildenafil. The cardiology database was searched for dogs with PH treated with sildenafil. PH was defined as systolic pulmonary arterial pressure (PAP_s) ≥25 mmHg at rest. Medical records were reviewed for the following information: signalment, duration and type of clinical signs before treatment, underlying disease, estimated or measured PAP_s, dosage and dosing interval of sildenafil, and the effect of treatment on clinical signs and pulmonary arterial pressure and survival time. Thirteen affected dogs were identified. Clinical signs included collapse, syncope, respiratory distress, and cough. Duration of clinical signs before presentation ranged from 3 days to 5 months. An underlying cause was identified in 8 dogs. The median sildenafil dosage was 1.9 mg/kg. Ten dogs received concurrent medications. Median PAP_s was 90 mmHg; 8 dogs were reevaluated after therapy, and the median decrease in PAP_s was 16.5 mmHg. The median survival time of all dogs was 91 days. Sildenafil appeared to be well tolerated in dogs with PH and was associated with decreased PAP_s and amelioration of clinical signs in most. Sildenafil represents a reasonable treatment option for dogs with pulmonary hypertension.

Key words: Collapse; Cor pulmonale; Hypoxemia; Pulmonary arterial pressure; Syncope; Viagra.

Pulmonary arterial hypertension (PH) is a pathologic condition characterized by abnormally high pressure in the pulmonary arterial circulation. Clinical signs associated with PH include tachypnea, respiratory distress, syncope, and right-sided heart failure. Pulmonary hypertension has been associated with a grave prognosis in dogs, with reported median survival times of 3.0 to 3.5 days after diagnosis.[1] This short survival time may be attributable to the fact that many dogs have refractory or severe respiratory distress and are euthanized because of their advanced disease state or oxygen dependency at the time of diagnosis.

Normal systolic pulmonary arterial pressure (PAP_s) is <25 mmHg at rest.[1–3] Pulmonary arterial pressure (PAP) may be measured directly by a catheter placed within the pulmonary artery. Alternatively, in the absence of pulmonic stenosis, PAP can be calculated indirectly with Doppler echocardiography and the modified Bernoulli equation. The Doppler technique requires regurgitant flow across the pulmonic or tricuspid valves to estimate diastolic or systolic pressure gradients, respectively.[4] Indirect Doppler estimation of PAP does not require anesthesia or specialized equipment, such as fluoroscopy, and is widely available in clinical practice. Standard evaluation of a dog identified with PH includes assessment for underlying disease or contributing causes of PH, including evaluation for pulmonary venous and left atrial hypertension (ie, congestive heart failure), pulmonary thromboembolic disease (eg, heartworm disease, Cushing's syndrome, protein losing nephropathy, or enteropathy), and chronic pulmonary disease (eg, chronic bronchitis or pulmonary fibrosis).[2,3] Treatment of severe PH has been notoriously unsuccessful, in part because many of the underlying causes of PH are not readily reversible. Common therapies that typically are directed toward the resultant cardiopulmonary disease include calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors, digoxin, and coagulation inhibitors.[1–3] In affected people, additional pharmacologic therapies include continuous infusion of prostacyclins (eg, epoprostenol),[5] endothelin antagonists (eg, bosentan),[6] and sildenafil.[7] Continuous infusions in veterinary medicine are impractical, and endothelin antagonists have yet to be evaluated in dogs with PH. Some human patients ultimately require lung transplantation.[5,8]

Sildenafil citrate is a highly selective phosphodiesterase type V inhibitor that results in increased concentrations of cyclic guanosine monophosphate, which subsequently results in nitric oxide–mediated vasodilatation.[5] Sildenafil decreases pulmonary arterial pressure and pulmonary vascular resistance in people with PH. Additionally, sildenafil may have effects on vascular remodeling.[7,8] Sildenafil has been used successfully to treat children and adults with pulmonary hypertension.[7,8–11]

The purpose of this retrospective study is to describe the clinical characteristics and outcome of dogs with pulmonary hypertension treated with sildenafil.

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Materials and Methods

The cardiology database at the Tufts Cummings School of Veterinary Medicine was searched for dogs with a diagnosis of pulmonary hypertension that were treated with sildenafil citrate.[a] Pulmonary hypertension is defined as a $PAP_s \geq 25$ mmHg at rest.[1–3] Medical records were reviewed for the following information: signalment, duration and type of clinical signs, and underlying disease (if identified). PAP_s was measured with pulmonary artery catheterization or echocardiography with Doppler. For echocardiographic estimation, the modified Bernoulli equation was used to estimate the pressure difference across the tricuspid valve, and this value was added to the estimated right atrial pressure. Right atrial pressure was estimated to be between 5 and 15 mmHg based on clinical and physical examination findings. The estimated right atrial pressure for dogs without right heart failure was 5 mmHg, and 10–15 mmHg was the estimated right atrial pressure in dogs with right heart failure, based on estimation of the level of jugular vein distension in sternal or standing body position. The dosage and dosing interval of sildenafil, the effect of treatment on clinical signs, PAP_s, systolic blood pressure, and survival time from diagnosis also were recorded. Clinical response to sildenafil was evaluated based on review of medical records and by subsequent interviews with the owners of the 10 dogs that were discharged from the hospital. Each owner was asked whether there was a change in the frequency of syncope, a change in cough frequency, or a change in the degree of respiratory difficulty. In addition, each owner was asked to evaluate whether their dog had experienced overall clinical improvement. Potential adverse effects (eg, systemic hypotension) were recorded. Dogs with pulmonic stenosis or right ventricular outflow tract obstruction were excluded.

Descriptive statistics were used including median and range for non-normally distributed data or mean and standard deviation for normally distributed results. A paired *t*-test was used to compare PAP_s, a Wilcoxon signed rank test was used to compare systolic blood pressure before and after sildenafil treatment, and Spearman's correlation was used to evaluate PAP_s and survival time.[b] Sildenafil citrate was used off label with informed client consent.

Results

Thirteen affected dogs were identified from April 2001 through October 2005. Eight dogs were spayed females, and 5 were castrated males. Dogs were 3 Shih-tzus, 2 Chihuahuas, 2 Golden Retrievers, and 1 each Cairn Terrier, Labrador Retriever, Maltese, Pug, Pekinese, and Fox Terrier. The median age at diagnosis was 14 years, 6 months (range, 4 years, 3 months to 15 years, 10 months). Median weight was 5.9 kg (range, 2.9 to 39.1 kg). Clinical signs recorded included collapse or syncope (8), cough (6), and respiratory distress (5). The duration of clinical signs ranged from 3 days to 5 months. The underlying cause was identified in 8 dogs and included chronic pulmonary disease (5), chronic valvular heart disease with mitral regurgitation and left-sided congestive heart failure (1), pulmonary overcirculation from patent ductus arteriosus (PDA) resulting in right-to-left shunting PDA (1), and pulmonary thromboembolism (1). The underlying cause of pulmonary hypertension could not be identified in 5 dogs, and primary PH was presumably diagnosed.

Sildenafil citrate[a] was administered PO at a median dose of 1.9 mg/kg (range, 0.5 to 2.7 mg/kg) at a dosing interval of every 8 to 24 hours. Ten dogs were treated with concurrent medications including angiotensin-converting enzyme inhibitor (6), furosemide (3), amlodipine (3), diltiazem (1), theophylline (3), phenobarbital (2), and antibiotics (2). Eight dogs received supplemental oxygen.

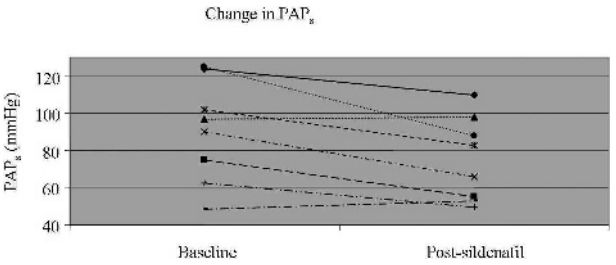

Fig 1. Graphical depiction of PAP_s at baseline and after administration of sildenafil ($P = .036$).

The PAP_s before therapy was measured directly in 2 dogs (102 and 89 mmHg) and estimated in 10 dogs at a mean of 98.5 mmHg (SD, 26.4 mmHg). A Doppler estimate of PAP_s was not available in the medical records and not found upon inspection of the saved echocardiographic recordings from the dog with the right-to-left PDA, although right-to-left shunting through the PDA was documented with ultrasound and the resting systemic arterial blood pressure was 90 mmHg.

Eight dogs had their estimated PAP_s rechecked after sildenafil therapy (Fig 1); 6 of the 8 dogs had a decrease in PAP_s. The median change for these 8 dogs was a decrease of 16.5 mmHg (range, increase of 4 mmHg to decrease of 37 mmHg) or 16.7%. The decrease in PAP_s was significant ($P = .036$). The median time between PAP_s reevaluation was 1.9 days (range, 1 hour to 112 days).

Systemic blood pressure was indirectly measured by Doppler in 11 dogs before treatment (median, 135/90 mmHg; range, 200/110 to 70/60 mmHg). Six dogs had their blood pressure measured after sildenafil treatment (median, 130/103 mmHg; range, 198/130 to 100/70 mmHg). After sildenafil therapy, systolic blood pressure decreased by a median 33 mmHg (range, increase of 58 mmHg to decrease of 60 mmHg). The change in blood pressure was not significant ($P = .25$). The median time between evaluation of blood pressure was 1.1 days (range, 0.3 to 2.0 days).

Three dogs were euthanized within 1 day of initiating sildenafil because of severe refractory respiratory distress. Ten dogs survived to discharge; 5 subsequently died, and 3 were euthanized because of progressive disease. Two dogs are still alive after 16 and 99 weeks; 1 diagnosed with chronic pulmonary disease and 1 with right-to-left PDA. The median survival time of all dogs, including those still alive, was 91 days (range, 1 to 693 days). Excluding the 3 dogs that were euthanized within 1 day of diagnosis, the median survival time of the remaining 10 dogs discharged from the hospital was 175 days (range, 28 to at least 693 days). The correlation of PAP_s at diagnosis and survival time (Fig 2) was not significant ($P = .99$).

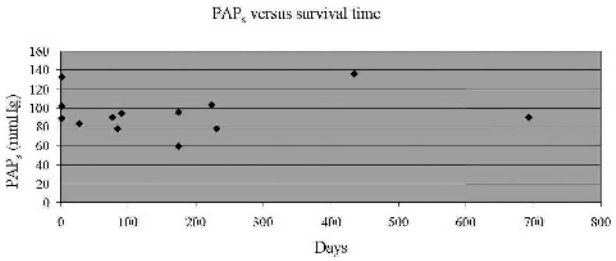

Fig 2. Scatter plot of survival in days versus systolic pulmonary arterial pressures ($P = .99$).

Two dogs had cardiogenic ascites; 1 dog had resolution of ascites. Of the 10 dogs discharged from the hospital, clinical progress was assessed by questioning the clients. Four of 6 dogs showed decreased coughing; 6 of 8, including the dog with right-to-left PDA, had a reduction in syncope; 8 of 10 had reduced respiratory effort; and 10 of 10 clients felt that overall their dogs were clinically improved.

Complications clearly associated with sildenafil therapy were uncommon. One dog was reported to have adverse gastrointestinal effects, but the dog was receiving 3 additional medications and the adverse gastrointestinal effects could not be solely attributed to sildenafil. Two clients reported cutaneous flushing in the inguinal region of their dogs; one did not experience this effect at lower sildenafil dosages. One dog that had marked improvement associated with sildenafil therapy, including resolution of ascites, received additional vasodilator (nitroglycerin paste) therapy at the primary veterinarian for respiratory distress; this dog subsequently died. The cost of the medication was of concern for 3 clients and led to temporary discontinuation in 1 dog.

Discussion

Sildenafil is a reasonable therapeutic option for treatment of PH in dogs. Sildenafil was generally well tolerated and associated with an improvement in clinical signs in most dogs. The median survival time in the dogs in this study was 91 days, whereas the survival reported in a retrospective study by Johnson et al was 3 days.[1]

The change in PAP_s after sildenafil was significant and similar to reports in people of decreased mean PAP of 11.1% to 12.5%.[12–14] Decreases in pulmonary vascular resistance and increases in cardiac output or index also consistently are reported in people after administration of sildenafil.[12–14] Pulmonary vascular resistance and cardiac output were not measured in these dogs. The time when PAP_s is rechecked may be relevant because sildenafil has a reported half-life ($T_{½}$) of 6.1 hours in dogs and a time to maximal concentration (T_{max}) of 1.1 hours.[15] Because this was a retrospective study, such information often was unavailable. Future studies should include evaluation of these variables as well as consistent timing of PAP_s reevaluation after sildenafil administration (ie, 2 to 4 hours post-drug administration).

Sildenafil was well tolerated in most dogs. However, 1 death may have occurred in association with concurrent nitrate therapy. Sildenafil is a highly selective inhibitor of type V phosphodiesterase, which is abundant in the pulmonary circulation and results in nitric oxide–mediated vasodilatation. Organic nitrates are nitric oxide donors, and lead to vasodilatation.[16] A combination of these 2 medications can lead to excess vasodilatation and frank hypotension, and their concurrent administration therefore is contraindicated.[17]

The observation of decreased systemic blood pressure in some of these dogs was interesting. Phosphodiesterase V has been revealed to be highly localized to 2 tissues, the corpus cavernosum and the vascular smooth muscle of lung; additionally, it has been shown that the activity of phosphodiesterase V in lung tissue is increased in PH.[18] Because of these reported findings, a decrease in systemic blood pressure would not be expected, and such is the case in several reports in people.[13,14,19] Differences between phosphodiesterase V inhibitors do exist; vardenafil decreased systemic and pulmonary vascular resistance similarly, whereas sildenafil and tadalafil had preferential effects on pulmonary vascular resistance.[19] The specific selectivity of phosphodiesterase V inhibitors is not known in dogs, and sildenafil could have an effect on systemic vascular resistance and blood pressure. The pre- and postsildenafil blood pressures measured during this retrospective study were obtained by different individuals with some degree of variability in technique, timing after sildenafil administration, or both. Systemic blood pressure, including baseline values, should be carefully monitored in dogs receiving sildenafil.

Cutaneous flushing in the inguinal region was reported in 2 dogs. This adverse effect (flushing) has been reported in people, as has headache, dyspepsia, dizziness, visual disturbances, nasal congestion, priapism, myalgia, and back pain.[11,17] These are adverse effects that would be difficult to recognize or document in veterinary medicine. However, a prescribing veterinary clinician should be aware of them.

A prospective, randomized, controlled trial is needed to further evaluate the effectiveness of sildenafil for canine pulmonary hypertension. Future studies should include consistently timed evaluations of PAP_s and evaluation of systemic blood pressure with respect to drug administration. Additional studies are needed to determine if sildenafil has an added benefit compared to other therapies for canine pulmonary hypertension. Additionally, this report was a retrospective study with inherent limitations, including many different concurrently prescribed medications, variable underlying disease processes, no control group, and a small sample size.

Overall, sildenafil was well tolerated in dogs with pulmonary hypertension. Combination therapy that included sildenafil in these dogs with pulmonary hypertension was associated with a statistically decreased PAP_s and improvement in clinical signs in most dogs. Sildenafil represents a reasonable treatment option in dogs with pulmonary hypertension, a disease for

which historically there have been few effective treatments.

Footnotes

[a] Viagra, Pfizer U.S. Pharmaceuticals, New York, NY
[b] SPSS version 11.5. SPSS Inc, Chicago, IL

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