Case Report

Therapeutic effects of sildenafil combined with low-dosage imatinib on pulmonary hypertension in five dogs

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Abstract

Five dogs were diagnosed with pulmonary hypertension (PH) secondary to chronic degenerative mitral valve disease or ventricular septal defect. They were initially administered low-dose imatinib mesylate (3 mg/kg, q24h) without changes to the background therapy to treat PH. The low-dose imatinib improved the right ventricular (RV) function parameters including estimated systolic and mean pulmonary arterial pressures (sPA and mPAP) and clinical symptoms. On day 53 to day 168 after imatinib administration, as PH and clinical signs worsened, low-dose sildenafil (0.5 mg/kg, q12h) was administered in combination with imatinib. This combination greatly reduced the estimated sPA and mPAP, and improved clinical symptoms and RV function parameters without worsening left ventricular function. A low-dose imatinib and sildenafil combination may provide a promising treatment alternative for canine PH.

Keywords: chronic degenerative mitral valve disease, Eisenmenger's syndrome, low-dose imatinib, pulmonary hypertension, sildenafil

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Introduction

Pulmonary hypertension (PH) is defined as systolic pulmonary artery pressure (sPA) of >30 mmHg or mean pulmonary arterial pressure (mPAP) of >20 mmHg (Reinero *et al*., 2020). The prognosis in dogs with PH is poor, with a median survival duration of 3–91 days after diagnosis (Bach *et al*., 2006). It is caused by pulmonary arterial vasoconstriction and vascular remodelling (Mandegar e*t al*., 2004). Imatinib, a tyrosine kinase inhibitor reverses pulmonary vascular remodelling (Leong *et al*., 2018b) and exhibits pulmonary vasodilatory effects in rats (Maihöfer *et al*., 2017). Therapy with low-dosage imatinib has improved clinical symptoms and echocardiographic outcomes without noticeable adverse effects in dogs with PH (Arita *et al*., 2013; Leong *et al*., 2018a). However, resistance to imatinib treatment may occur in PH patients as a result of the relationship between apoptosis and plasma PDGF levels (Nakamura *et al*., 2012). In such cases, imatinib therapy combined with other agents specific for PH may be required.

Sildenafil is a selective phosphodiesterase type 5 inhibitor that relaxes vascular smooth muscle and lowers pulmonary vascular resistance (Kiss *et al*., 2014). It reduces sPA and improves clinical signs in PH dogs (Bach *et al*., 2006; Brown *et al*., 2010; Kellihan and Stepien, 2012), but there are some reports that it only slightly reduces sPA (Kellum and Stepien, 2007; Saetang and Surachetpong, 2020). It may be important to further investigate combination therapies of sildenafil and other drugs to ensure the reduction of sPA in PH dogs.

A combination of low-dosage imatinib and sildenafil is reportedly effective in treating PH in rats (Jasińska-Stroschein *et al*., 2015). Pharmacokinetic interactions between imatinib and sildenafil in patients with severe PH have also shown that sildenafil concentrations increased an average of 64% in the presence of imatinib without an increased risk of liver toxicity (Renard *et al*., 2015). Therefore, a combination of low-dosage imatinib and sildenafil may be a better regimen for treating PH in dogs. This case report represents therapeutic effects of low-dosage imatinib in combination with sildenafil for PH secondary to chronic degenerative mitral valve disease (CDMVD) in four dogs and ventricular septal defect (VSD) in one dog.

Case description

Patient signalment, etiology, history and clinical findings are summarized in Table 1. A diagnosis of PH was defined as sPA of >30 mmHg or mPAP of >20 mmHg (Reinero et al. 2020), which were calculated using the modified Bernoulli equation. Cases 1–4 were diagnosed with PH secondary to CDMVD, and case 5 with PH due to VSD with Eisenmenger's syndrome. Each case was classified as ISACHC IIIa or IIIb and ACVIM stage C or D. The clinical symptoms of the dogs were subjectively assessed. The dogs presented with a cough, respiratory distress, exercise intolerance and/or syncope despite being treated with polypharmacy approaches. Case 2 had ascites and edema.

In all dogs with severe PH, low-dosage imatinib mesylate (Glivec; Novartis Pharma, Tokyo), 3 mg/kg, PO, q24h, was initially administered. All dogs continued to receive previous medications without changes. On day 53–168 after imatinib administration, PH and clinical signs re-worsened. Subsequently, sildenafil (Levatio; Viatris, Tokyo) at a low-dosage (0.5 mg/kg, PO, q12h) was administered in combination with low-dose imatinib. A full series of work-ups including physical examination, hematology and blood biochemistry, chest radiography and echocardiography were performed prior to imatinib administration (pre-0; day 0), 1 and 3 months after its administration; before sildenafil + imatinib administration (pre-1) and 1 and 3 months after its administration. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration was measured using an enzyme-linked immunosorbent assay at a reference laboratory (IDEXX Laboratories, Tokyo). Key echocardiographic parameters were measured using transthoracic two-dimensional, M-mode and pulsed, continuous wave and tissue Doppler echocardiography, as reported previously (Arita *et al*., 2013). In the apical 5-chamber view, a pulsed-wave sample volume was placed just under the aortic valve and the cross-sectional area of the left ventricular (LV) outflow tract, aortic ejection flow velocity and time velocity integral were measured, and stroke volume (SV) was calculated. Cardiac output (CO) was calculated as SV × heart rate (HR). The mPAP was estimated using the following equation: 4 × (the early diastolic pulmonary regurgitation velocity)^2. Left atrium/aorta (LA/Ao) and right atrium/aorta (RA/Ao) ratios were selected as indices of LA and RA pressure load, respectively. The Tei index was chosen to evaluate both systolic and diastolic functions of the LV or right ventricle (RV). The LV fractional shortening, ratio of peak velocity of early diastolic transmitral flow wave to peak velocity of early diastolic mitral annular motion (E/Em) and tricuspid annular plane systolic excursion (TAPSE) were selected to evaluate LV contractility, LV dilatation function and RV contractility, respectively. For simplicity, data is shown as mean ± standard deviation (SD) in the tables.

Clinical symptoms including cough, exercise intolerance and syncope were reduced at 1 month after imatinib administration compared with pre-0. Although clinical signs in all cases worsened on day 53–168 after imatinib administration, they improved at 1–3 months after imatinib + sildenafil administration compared with that at pre-0 or pre-1. Ascites were observed at pre-0 and pre-1 in case 2 only but both disappeared 1–3 months after imatinib or imatinib + sildenafil administration.

Radiographic, echocardiographic, circulation and cardiac biomarker variables are shown in Table 2. In cases 1–4, elevated sPA (mean 93.0 mmHg) at pre-0 decreased at 1 month (mean 59.0 mmHg; decrease of 37%) after imatinib administration. Moreover, sPA decreased at 1 and 3 months (mean 52.3 and 65.8 mmHg, respectively) after imatinib + sildenafil administration compared with pre-0 or pre-1 value (mean 100.3 mmHg). The largest decrease in sPA was seen at 1 month after imatinib + sildenafil

administration (44% and 48% decrease from pre-0 and pre-1 values). In cases 1, 2 and 5, mPAP also decreased at 1 month after imatinib + sildenafil administration compared with pre-1 value. In case 5 with VSD, elevated mPAP (109 mmHg) at pre-1 was reduced 24% (to 83 mmHg) at 3 months after imatinib + sildenafil administration.

Vertebrae heart size, RA/Ao ratio, RV Tei index, maximum tricuspid regurgitation velocity (TRmax), end-diastolic pulmonary regurgitation maximum velocity (PRmax) decreased at 1–3 months after imatinib administration compared with pre-0, whereas CO and TAPSE values increased at 1 month after imatinib administration (Table 2). TAPSE decreased in pre-1 compared with pre-0. After imatinib + sildenafil administration, HR, RA/Ao ratio, RV Tei index and TRmax decreased at 1–3 months compared with pre-0 or pre-1, whereas TAPSE increased at 1–3 months compared with pre-0 or pre-1 (Table 2).

NT-proBNP concentration (reference range: <900 pmol/L) was elevated at pre-0 but decreased at 1 month after imatinib administration and did not increase at 1–3 months after imatinib + sildenafil administration (Table 2). Case 5 with VSD had polycythemia, which did not further deteriorate with imatinib + sildenafil administration. No blood biochemical changes suggestive of hepatic or renal failure were observed by imatinib or imatinib + sildenafil therapies. On day 353, 417,148 and 1088 after imatinib administration, four dogs (cases 1–4) died of congestive heart failure. Case 5 tolerated well low-dose imatinib + sildenafil without adverse effects, and is alive on day 2349 after imatinib administration.

Discussion

The rationale for using low-doses of imatinib (3 mg/kg) in dogs has been outlined in previous studies (Arita *et al*., 2013). Canine cases in this study had more severe PH (estimated sPA = 93.0 ± 8.2 mmHg, mean ± SD) than the cases with PH (estimated sPA = 45.7 ± 16.2 and 63.3 ± 24.9 mmHg) in previous studies (Arita *et al*., 2013; Leong *et al*., 2018a). In this report, low-dosage imatinib reduced sPA and mPAP and improved RV function parameters without worsening LV function and improved clinical symptoms. These findings agreed with those in a previous study (Arita *et al*., 2013). However, PH and clinical symptoms in all cases were found to deteriorate from 53 to 168 days (median 138 days) after imatinib medication. This period seemed to be slightly shorter than that in a previous report (Leong *et al*., 2018a). This may be the result of canine cases in this study having more severe PH and higher ISACHC severity than cases in previous studies (Arita *et al*., 2013; Leong *et al*., 2018a). On the other hand, when PH worsened at 53–168 days after imatinib medication, TAPSE at that time (pre-1) decreased compared with the value before imatinib administration (pre-0). This decrease in TAPSE may be due to the reduction of RV contraction associated with the deterioration of PH. In addition, resistance to imatinib treatment may be involved in this event.

This study showed that in four dogs with PH due to CDMVD, the combination of low-dosage sildenafil and imatinib largely reduced the estimated sPA by an average 48% (from average 100.3 mmHg at pre-1 to average 52.3 mmHg at post 1 month) and improved clinical symptoms. In addition, the elevated mPAP due to CDMVD and VSD was reduced by an average 29% (from average 56.2 mmHg at pre-1 to average 40.1 mmHg at post 1 month). These decreases in estimated sPA and/or mPAP after administration of low-dose imatinib and sildenafil combination were apparently greater than those found in previous studies after administration of sildenafil alone at larger dosages (Bach *et al*., 2006; Kellum and Stepien, 2007; Brown *et al*., 2010; Saetang and Surachetpong, 2020). Additionally, this combination improved RV function parameters without diminishing LV function. These results agreed with a report that a combination of low-dosage imatinib and sildenafil was effective in treating PH in rats (Jasińska-Stroschein et al., 2015). These effects may be due to pulmonary vasodilatory activity through pulmonary vascular relaxation and antiremodeling effects of sildenafil (Kiss *et al*., 2014) and pulmonary vasodilatory activities in addition to inhibition of pulmonary vascular remodeling by imatinib (Maihöfer *et al*., 2017; Leong *et al*., 2018b). Pharmacokinetic interactions between imatinib and sildenafil might have resulted in additive effects of both agents in this study (Jasińska-Stroschein *et al*., 2015; Renard *et al*., 2015).

Median survival time in dogs with severe PH has been previously reported to be 3–91 days (Bach *et al*., 2006). Furthermore, a recent study reported that the median survival time in dogs with PH secondary to CDMVD stage C was 368 days (Udomkiattikul *et al*., 2022). Cases in this report had a longer survival time (median 417 days, range 148 to >2439 days after imatinib medication; median 249 days, range 95 to >2301 days after imatinib + sildenafil medication) than those found in previous studies. Thus, the use of a low-dosage imatinib and sildenafil combination may be effective in prolonging the survival of dogs with severe PH. No apparent clinical side effects associated with low-dose imatinib and sildenafil combination were found in the present cases, suggesting that this combination may be used safely for long-term therapy in dogs with PH.

In conclusion, the combined administration of low-dose imatinib and sildenafil markedly reduced the estimated systolic pulmonary arterial pressure by an average 48% at 1 month and improved RV function and clinical symptoms in five dogs with severe PH. This is the first report suggesting the effectiveness of low-dosage imatinib and sildenafil combination for treating dogs with PH.

Conflict of interest: The authors have no conflict of interest.

Table 1 Patient signalment, aetiology, history and clinical findings.

Case	1	2	3	4	5
Breed	Pomeranian	Chihuahua	Chihuahua	Maltese	Miniature Dachshund
Age (y)	13	11	11	9	0.5
Sex	Male castrated	Male castrated	Male intact	Male castrated	Female intact
BW (kg)	3.3	3.3	2.1	5.4	3.7
Etiology of PH	Pulmonary venous PH due to MI	Pulmonary venous PH due to MI	Pulmonary venous PH due to MI	Pulmonary venous PH due to MI	Pulmonary arterial PH due to VSD
Clinical signs	Syncope, cough, exercise intolerance	Cough, exercise intolerance, ascites	Syncope, cough, exercise intolerance	Syncope, cough, exercise intolerance	Syncope, exercise intolerance
Auscultation findings	Grade V/VI left murmur, grade III/VI right murmur	Grade V/VI left murmur, grade III/VI right murmur	Grade IV/VI left murmur, grade III/VI right murmur	Grade IV/VI left murmur, grade III/VI right murmur	Grade I/VI left murmur
Thoracic radiograph findings	VHS:12.9, left atrial enlargement, bronchial compression, perihilar pulmonary edema	VHS:15.0, left atrial enlargement, bronchial compression, perihilar pulmonary edema	VHS:13.7, left atrial enlargement, bronchial compression, perihilar pulmonary edema	VHS:14.5, left atrial enlargement, bronchial compression, perihilar pulmonary edema	VHS:9.8, right heart enlargement, dilation of main pulmonary artery
ISACHC severity	Ⅲa	Ⅲb	Ⅲb	Ⅲa	Ⅲa
ACVIM stage	C	D	C	C	–
History of medications	Alacepril (1.8 mg/kg, q12h), pimobendan (0.37 mg/kg, q12h), furosemide (2.0 mg/kg, q12h) for 2 y	Alacepril (1.8 mg/kg, q12h), pimobendan (0.37 mg/kg, q12h), furosemide (1.5 mg/kg, q12h) for 9 mo	Alacepril (3.0 mg/kg, q12h), pimobendan (0.30 mg/kg, q12h), furosemide (2.0 mg/kg, q12h) for 1 y	Alacepril (1.1 mg/kg, q12h), pimobendan (0.37 mg/kg, q12h), furosemide (2.0 mg/kg, q12h) for 1 y	Pimobendan (0.17 mg/kg, q12h) for 1 mo
Imatinib therapy (day)	167	168	53	113	138
Imatinib+sildenafil therapy (day)	186	249	95	975	2301

PH, pulmonary hypertension; ISACHC, International Small Animal Cardiac Health Council; ACVIM, American College of Veterinary Internal Medicine; MI, mitral valve insufficiency; VSD, ventricular septal defect; VHS, vertebrae heart size.

Table 2 Radiographic, echocardiographic, circulation and cardiac biomarker variables (mean ± SD)

Variables	After imatinib (months)			After imatinib + sildenafil (months)		
	Pre-0 (n = 5)	1 (n = 5)	3 (n = 4)	Pre-1 (n = 5)	1 (n = 5)	3 (n = 4)
Heart rate (beats/min)	151±22	137±26	143±29	160±17	134±15†	150±7
Mean blood pressure (mmHg)	123±19	123±18	106±22	114±22	134±27	125±14
Vertebrae heart size	13.2±2.1	12.7±1.7	12.6±2.3*	13.4±1.7	12.8±2.0	12.8±1.9
Left atrium/aorta	2.57±1.14	2.32±0.84	2.20±0.91	2.39±1.01	2.10±0.89†	2.05±0.78
Right atrium/aorta	1.90±0.63	1.14±0.29*	1.33±0.25	1.63±0.19	1.24±0.15††	1.46±0.28
LV fractional shortening (%)	42.5±12.4	46.0±12.8	49.1±8.2	50.3±3.2	44.5±11.5	51.5±7.6
Normalized end-diastolic LV inner dimension	2.0±0.5	2.3±0.7	1.9±0.7	2.0±0.5	2.0±0.5	1.8±0.7
E/Em	10.6±4.3	10.2±4.1	14.6±6.3	13.1±5.5	11.6±2.8	8.9±4.5†
Cardiac output (L/min)	0.672±0.248	1.157±0.424*	0.747±0.196	0.548±0.148	1.029±0.717	0.676±0.396
Left Tei index	0.400±0.260	0.293±0.218	0.437±0.179	0.533±0.187	0.372±0.245	0.501±0.282
Right Tei index	0.586±0.090	0.327±0.105*	0.438±0.254	0.554±0.263	0.256±0.172*†	0.382±0.125*
Maximum systolic mitral regurgitation velocity (cm/s)	644±76	579±50	573±61	574±60	604±89	639±83
Maximum tricuspid regurgitation velocity (cm/s)[a]	455±22	348±54*	355±90	475±26	316±81*†	370±57†
End-diastolic pulmonary regurgitation maximum velocity (cm/s)[b]	358±131	342±130*	337±121	383±142	284±159	223±33
Tricuspid annular plane systolic excursion (mm)	9.3±3.6	13.9±5.2**	10.9±5.4	6.8±2.3*	13.3±5.2**†	12.4±5.8†
Estimated systolic pulmonary arterial pressure (mmHg)[a]	93.0±8.2	59.0±14.5*	61.5±22	100.3±10.0	52.3±21.0*†	65.8±16.4*†
Estimated mean pulmonary arterial pressure (mmHg)[b]	54.6±37.4	50.2±35.6	48.3±32.6	56.2±45.8	40.1±41.0†	46.3±33.3
Serum N-terminal probrain natriuretic peptide (pmol/L)	3004±1758	2357±1793**	2591±1585	4065±3097	3579±3787	3928±3035

Pre-0, before imatinib administration; Pre-1, before imatinib + sildenafil administration; LV, left ventricular; E/Em, ratio of peak velocity of early diastolic transmitral flow wave to peak velocity of early diastolic mitral annular motion; [a] $n = 4$; [b] $n = 3$.

*$P<0.05$, **$P<0.01$ versus Pre-0; †$P<0.05$, ††$P<0.01$ versus Pre-1 by Shapiro–Wilk test followed by paired *t*-test or Wilcoxon signed rank test.

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