Thesis for the degree of Master of Veterinary Medicine

Clinical Application of Tadalafil in Dogs with Pulmonary Hypertension

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Abstract

Pulmonary hypertension (PH) is defined as abnormally increased pressure within the pulmonary vasculature. Phosphodiesterase type 5 (PDE5) inhibitors are used to manage PH. Tadalafil, which is a PDE5 inhibitor with a longer half-life than sildenafil, is usually selected as the first line PDE5 inhibitor, has rarely been studied. To analyze and report information on veterinary patients who used tadalafil as a treatment for PH at the Veterinary Medical Teaching Hospital, Jeju National University. Patients and materials: This retrospective study evaluated patients with a history of tadalafil use during their visits to the Veterinary Medical Teaching Hospital of Jeju National University from January 2021 to July 2023. A total of 11 dogs tentatively diagnosed with PH received tadalafil, with an initial dosage of 1 mg/kg once daily were included in the study. The monitoring period was >4 weeks, and the evaluation of side effects and efficacy (remission versus non-remission) was based on history taking and physical examination. Among the 11 dogs included, 10 were treated with tadalafil after sildenafil, and only one dog was treated with tadalafil as the first choice. Adverse effects, including nausea, were observed in one dog. Clinical efficacy resulted in remission in seven dogs (complete to partial) and non-remission in four dogs. Tadalafil is effective and tolerated in dogs at a daily dose of 1 mg/kg, and could be

considered an attractive alternative to sildenafil in terms of increasing the interval between doses.

Keywords: Tadalafil, PDE5 inhibitor, Sildenafil, Pulmonary hypertension, Dog

Ⅰ. Introduction

PH is the abnormally increased pressure within the pulmonary vasculature caused by increased pulmonary blood flow, increased pulmonary vascular resistance, increased pulmonary venous pressure, or a combination thereof [14]. In human medicine, PH is defined as a mean pulmonary arterial pressure (mPAP) of > 20 mmHg at rest, which is directly assessed by right heart catheterization (RHC) [9]. However, in veterinary medicine, as RHC is not routinely performed, echocardiographic evaluation is considered for patients with PH-related clinical symptoms to assess the probability of PH [14]. In humans, PH is classified into five groups according to the underlying diseases, namely, pulmonary arterial hypertension (Group I), left heart disease (Group 2), lung diseases and/or hypoxia (Group 3), pulmonary arterial obstruction such as chronic pulmonary thromboembolism or others (Group 4), and unclear and/or multifactorial mechanisms (Group 5) [9]. In contrast, PH in dogs also includes a sixth groups which includes PH due to parasitic diseases, particularly heartworm infections [14].

In dogs, clinical signs related to PH include syncope, tachypnea, respiratory distress, increased respiratory effort at rest, prolonged post-activity tachypnea, right-sided heart failure, and cyanotic or pale mucous membrane [14]. In addition, to assess the probability of PH, specific echocardiographic parameters can be evaluated, including peak tricuspid regurgitation velocity (TRV) (m/s) and other echocardiographic signs which suggest right heart enlargement and/or dilation of adjacent blood vessels [14].

The treatment of PH includes management of the underlying disease and medication [9, 14]. In human medicine, there is a wide range

of drugs with different mechanisms, among which PDE5 inhibitors are recommended as first-line use, and changed to drugs with other mechanisms or used in combination if symptoms are not well managed with PDE5 inhibitors alone [14]. PDE5 inhibitors act by regulating the intracellular concentration of cyclic guanosine monophosphate (cGMP), which is involved in the nitric oxide pathway and plays a key role in smooth muscle cell relaxation [4, 21]. When the intracellular cGMP levels increase, cGMP binds to PDE5, and thus the cGMP concentration is lowered, which interferes with this action by competitively binding to PDE5 inhibitors, which are structurally similar to cGMP, at the binding site of cGMP on PDE5 [4, 21].

There are two PDE5 inhibitor drugs currently used in veterinary medicine, which are sildenafil and tadalafil [14]. Of these, sildenafil is usually selected as the first-line PDE5 inhibitor to treat PH and has been studied extensively, whereas tadalafil has been newly introduced and with a limited number of studies [14]. Therefore, this retrospective study aimed to analyze and report information on veterinary patients treated with tadalafil for PH at the Veterinary Medical Teaching Hospital, Jeju National University.

Ⅱ. Materials and Methods

1. Animals, inclusion and exclusion criteria

The electronic medical records (EMRs) of the Veterinary Medical Teaching Hospital of Jeju National University were searched using the keyword, “tadalafil”. Records from January 2021 to July 2023 were evaluated and data on patients with a history of tadalafil use collected. The patient inclusion criteria were client-owned dogs diagnosed with PH and a history of tadalafil therapy. Dogs treated with tadalafil for <4 weeks or insufficient chart information for PH diagnosis or suspicion were excluded.

2. PH diagnosis

The diagnostic criteria for PH were based on the American College of Veterinary Internal Medicine (ACVIM) consensus statement for canine PH. Dogs showing clinical signs related to PH received an echocardiographic evaluation of the right parasternal and left apical views to estimate peak TRV (m/s) and anatomic signs of PH were considered and then evaluated for the echocardiographic probability of PH, which was performed by veterinarians under the guidance of a specialist, who is a diplomat of the Korean College of Veterinary Internal Medicine (DKCVIM).

Dogs with PH were then classified into the following six groups depending on the underlying diseases that caused PH: Group 1, pulmonary arterial hypertension; Group 2, left heart disease; Group 3, respiratory disease, hypoxia, or both; Group 4, pulmonary thromboembolism; Group 5, parasitic disease (i.e., heartworm infection); and Group 6, multifactorial or unclear mechanisms.

3. Tadalafil administration and monitoring

For dogs with a history of tadalafil use for PH management, the initial dose of tadalafil was 1 mg/kg q24h (Gugu-tablet; Hanmi Pharmaceutical Co.). Evaluation of the adverse effects and clinical efficacy of tadalafil administration was based on patient history and physical examination.

Ⅲ. Results

A total of 16 dogs were diagnosed with PH and had a history of tadalafil administration were identified on the keyword search and enrolled. Among them, five dogs were excluded for the following reasons: dosing period of tadalafil within 4 weeks (n = 4) and insufficient chart information to suspect PH (n = 1) (Figure 1). As a result, 11 dogs were included in the study with signalment features described in Table 1. The patients had a mean age of 11.2 years (7.0-15.1 years), a mean body weight of 6.0 kg (2.2-25.2 kg), and a sex distribution consisting of five castrated males and six spayed females. Except for a single dog (Alaskan malamute), 10 dogs were small breeds, including Maltese, Shih-tzu, Pomeranian, toy poodle, and pug. Eleven dogs had underlying diseases such as atrioventricular block (n = 2), chronic kidney disease (n = 4), cognitive dysfunction syndrome (n = 2), chronic pancreatitis (n = 1), pyoderma (n = 1), urethral calculi (n = 1), perineal hernia (n = 1), proteinuria (n = 1), gallbladder mucocele (n = 2), and keratoconjunctivitis sicca (n = 1) (Table 2).

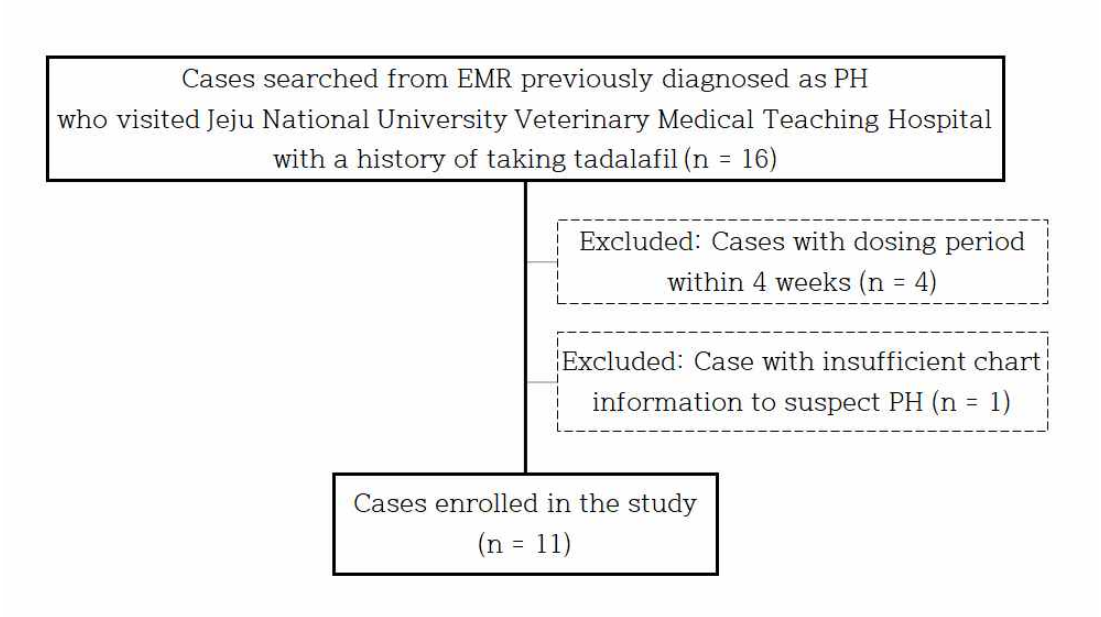

Figure 1. Case selection. Among 16 dogs previously diagnosed as PH with a history of tadalafil administration on EMRs, five dogs were excluded. Four dogs had a dosing period of tadalafil within 4 weeks and one dog had insufficient chart information to suspect PH.

Table 1. Signalments of 11 dogs

	Age (years)	Sex	Breed	Body weight (kg)
Dog 1	13	Female spayed	Poodle	4.6
Dog 2	13	Female spayed	Shih-tzu	5.2
Dog 3	7	Male castrated	Maltese	3.5
Dog 4	8	Male castrated	Maltese	2.3
Dog 5	15	Female spayed	Pomeranian	3.2
Dog 6	12	Male castrated	Pomeranian	3.7
Dog 7	11	Female spayed	Maltese	5.4
Dog 8	13	Female spayed	Poodle	4.4
Dog 9	12	Female spayed	Pug	6.2
Dog 10	9	Male castrated	Pomeranian	2.2
Dog 11	10	Male castrated	Alaskan malamute	25.2
Mean	11.2			6.0

Table 2. Concurrent diseases of 11 dogs

	Concurrent diseases
Dog 1	Atrioventricular block, chronic kidney disease
Dog 2	Chronic pancreatitis, chronic kidney disease, cognitive dysfunction syndrome
Dog 3	None
Dog 4	None
Dog 5	Pyoderma, cognitive dysfunction syndrome
Dog 6	Urethral calculi, perineal hernia, chronic kidney disease
Dog 7	Chronic kidney disease, proteinuria, gallbladder mucocele
Dog 8	Gallbladder mucocele
Dog 9	Atrioventricular block, keratoconjunctivitis sicca
Dog 10	None
Dog 11	None

The clinical symptoms related to PH are demonstrated in Table 3. The dogs were classified into six groups according to the underlying disease that caused PH: Group 2 (n = 2), Group 3 (n = 5), Group 4 (n = 1), and Group 6 (n = 3), notably, both left heart and respiratory diseases contributed to the occurrence of PH.

Table 3. PH-related clinical signs and PH classification of 11 dogs

	Clinical signs	PH groups
Dog 1	Syncope	2
Dog 2	Syncope	2
Dog 3	Syncope, respiratory effort	6
Dog 4	Syncope, respiratory distress at rest	6
Dog 5	Syncope, respiratory effort at rest	3
Dog 6	Tachypnea, prolonged-post exercise tachypnea	3
Dog 7	Tachypnea	3
Dog 8	Respiratory distress	3
Dog 9	Syncope, respiratory distress	3
Dog 10	Tachypnea, respiratory distress	6
Dog 11	Respiratory effort, right-sided heart failure	4

Regarding tadalafil administration, 10 dogs were converted from sildenafil, with one patient receiving tadalafil as the first choice due to the side effects associated with sildenafil. The patients were switched to tadalafil due to the insufficient effect of sildenafil (n = 7), for convenience (increased administration intervals (n = 2)), and unknown (n = 1). Among the 10 dogs, only one dog with sildenafil side effects had a washout period of sildenafil.

The initial dosage of tadalafil was 1 mg/kg q24h in 11 dogs, and 7 dogs received dosage control or discontinuation of the drug due to insufficient efficacy or adverse events. The final mean dosage was 1.18 mg/kg q24h, ranging from 1 mg/kg q48h to 1.5 mg/kg q24h. The mean administration period was 274 days (range, 28-685 days). For two dogs whose final administration period was difficult to confirm due to the loss to follow-up information, the administration period was calculated until the last visit date.

Adverse effects of tadalafil (nausea) were observed in only one dog, which persisted for a while, even though the dosage of the drug was reduced. According to the history of clinical symptoms, seven dogs showed clinical remission (from partial to complete), while the other four dogs showed no remission of clinical symptoms.

Ⅳ. Discussion

In human medicine, the PDE5 inhibitors sildenafil, tadalafil and vardenafil have been studied as PH therapeutic drugs [2]. Among them, vardenafil has been used more recently; thus, its clinical efficacy and safety have recently been demonstrated [11, 12]. Sildenafil and tadalafil are the mainly used to treat PH in humans and are mentioned in the European Society of Cardiology/European Respiratory Society guidelines [9]. The rate of mention and frequency of use of sildenafil were overwhelmingly higher than those of tadalafil, which may be due to differences in the timing of drug development.

Sildenafil, developed by Pfizer (New York, United States) in 1986, was approved by the Food and Drug Administration (FDA) as a treatment for erectile dysfunction under the product name Viagra® in 1998, and by the FDA in 2005 as a treatment for pulmonary arterial hypertension under the product name Revatio®. Tadalafil, developed by Eli lily and company (Indiana, United States) in 2003, has been applied as a PH treatment since 2009, when was licensed by the FDA as a treatment for pulmonary arterial hypertension under the product name Adcirca® in 2009. Therefore, owing to this difference in development time, sildenafil has been studied more extensively and is more commonly used [8, 16, 19]. In the ACVIM consensus, sildenafil has been well studied and is commonly used to treat canine PH. However, tadalafil is a relatively recent drug with advantages as an alternative to sildenafil [14].

In humans, several studies have been conducted on the clinical tolerance and efficacy of switching from sildenafil to tadalafil in patients [1, 6, 13, 15, 17, 18, 20]. In one study, the reasons for converting sildenafil to tadalafil included the convenience of increasing the

administration interval, insufficient efficacy of sildenafil, adverse effects of sildenafil, and cost problems [6]. Among these reasons, the most attractive is the convenience of longer dosing intervals than sildenafil, which is supported by the longer half-life of tadalafil compared to sildenafil [3]. The reasons for conversion in our retrospective study were similar to those reported in previous studies.

In humans, the European Society of Cardiology & European Respiratory Society (ESC/ERS) guidelines for PH recommend that risk assessment be conducted using the World Health Organization (WHO) functioning class, 6-minutes walking test, and blood concentration of BNP or pro-BNP as prognostic factors when evaluating the prognosis of patients with PH [5, 9]. In veterinary medicine, PH prognosis is evaluated mainly by monitoring clinical symptoms, whereas monitoring echocardiographic parameters is not essential as they may not be consistent with changes in clinical symptoms [14]. Therefore, our retrospective study also evaluated the progress of treatment by monitoring clinical symptoms.

A previous pilot study compared the clinical efficacy of tadalafil and sildenafil in canine PH, where 11/21 dogs were administered tadalafil at a dose of 2 mg/kg q24h [10]. As a result, there was a significant improvement in the quality of life, while hemodynamic parameters showed no significant improvement [10]. There was also no significant difference in efficacy between sildenafil and tadalafil, and adverse effects were observed in five dogs [10]. Compared to this previous study, there were differences with our study, including an initial dosage of 1 mg/kg q24h, a monitoring period of at least 4 weeks, and a lower frequency of side effects. The lower incidence of adverse effects in our study may be due to the administration of a lower dose of tadalafil.

Four dogs (#1, 5, 6, and 11) did not show clinical remission,

which may have been to an underlying disease which was not sufficiently managed, or another underlying disease that may have caused the symptoms to occur concurrently. In Dog 1, there was insufficient remission due to myxomatous mitral valve degeneration with atrioventricular block, which seems to be another cause of syncope. In Dog 5, due to its breed-specific nature, it is assumed that the narrow brachycephalic airway itself continuously causes hypoxia, inhibiting the adequate management of symptoms. Dog 6 was suspected to have laryngopharyngeal disease as the cause of non-remission of clinical symptoms, but the owner did not agree to intensive examination for diagnosis. Finally, Dog 11 had pulmonary thromboembolism as an underlying disease of PH and was nonresponsive to thromboprophylactic agents.

The limitations of this study are: 1) the small sample size; 2) the nature of retrospective research, such as differences in treatment processes, such as drug dosage control among different clinicians and insufficient chart information; 3) differences in administration methods, which may have affected the results: and 4) failure to quantify the degree of clinical efficacy. As mentioned, ACVIM consensus suggests that PH prognosis should be evaluated mainly by monitoring clinical symptoms, and it is also said that Function EvaluaTion of Cardiac Health (FETCH) scoring could be beneficial [7, 14]. The previous pilot study used FETCH scoring so that they could quantify the clinical efficacy [10]. In our study, however, there was insufficient medical records to use FETCH scoring or create our own scoring criteria. Therefore, studies on consistent therapeutic applications and the quantitative evaluation of clinical efficacy using a larger population and various dosages of the drug are needed.

Ⅴ. Conclusion

In this study, among 11 dogs, 10 dogs were small breeds except 1 alaskan malamute, and all of them started tadalafil administration with 1 mg/kg q24h. And some dogs received dosage control or discontinuation of the drug, with a dose range from 1 mg/kg q48h to 1.5 mg/kg q24h. An adverse effect showed in 1 dog, and 7 dogs showed clinical remission in contrast to 4 dogs whose underlying disease was poorly managed or other concurrent disease contributed to non-remission of clinical symptoms.

In conclusion, this study showed that in PH dogs with mainly small breeds, if the underlying disease is properly managed, tadalafil administration with 1 mg/kg q24h might be well-tolerated, effective, and more convenient than sildenafil with longer interval.

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폐고혈압이 있는 개에서 타달라필의 임상적 적용

이 새 영

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요약

폐고혈압은 폐혈관 내 압력이 비정상적으로 증가한 것으로 정의되며, 포스포디에스테라제 5형 억제제는 폐고혈압을 관리하는 데 사용되는 약물이다. 일반적으로 포스포디에스테라아제 5형 억제제의 첫 번째 옵션으로 선택되는 실데나필보다 반감기가 긴 또 다른 포스포디에스테라아제 5형 억제제인 타달라필은, 임상적 효능이나 부작용에 관해 연구된 바가 굉장히 적다. 따라서, 제주대학교 동물병원에 내원한 환자 중 폐고혈압 치료를 위해 타달라필을 복용한 이력이 있는 환자들에 대한 정보를 공유하고자 전자의무기록을 기반으로 본 후향적 연구를 진행하였다. 2021년 1월부터 2023년 7월까지, 미국 수의내과학협회에서 발표한 개 폐고혈압 합의문에 제시된 진단기준에 근거하여, 폐고혈압과 관련된 임상증상을 보인 환자들을 대상으로, 심장초음파 검사를 통해 폐고혈압 가능성을 평가하여 잠정적으로 진단하였다. 그 결과, 폐고혈압 치료를 위해 타달라필을 복용한 16마리 중 복용 기간이 4주 이내로 짧은 4마리와 폐고혈압을 의심할 만한 차트 정보가 부족한 한 마리를 제외하고 최종적으로 11마리에 관한 연구를 진행하였으며, 타달라필 최초복용 용량은 모두 체중 당 1 밀리그램 일 1회로 동일했다. 최소복용기간은 4주로 하였으며, 부작용 및 효능 평가는 문진과 신체검사를 통해 이루어졌다. 임상적 효능은 완화 또는 효과없음으로 분류되었다. 타달라필 약물 선택에 있어서, 1마리의 개가 포스포디에스테라아제 5형 억제제의 첫 번째 선택으로 타달라필을 복용했던 경우를 제외하고, 10마리는 모두 실데나필에서 타달라필로 전환된 경우였다. 그 결과

11마리의 개중 7마리에서 타달라필 용량 조절 또는 단약을 보였고, 한 마리가 부작용으로 오심증상을 보였다. 7마리의 개에서 임상적 완화를 보였고, 4마리의 개에서 효과가 없는 것으로 평가되었다. 결론적으로, 작은 표본 크기 및 후향적 연구 특성상 일부 한계에도 불구하고, 본 연구를 통해, 소형견 위주의 폐고혈압 환자에서, 기저질환이 적절하게 관리된다면, 타달라필 체중 당 1 밀리그램 일 1회 복용은 효과적이고 안전하였으며, 또한 실데나필보다 투약 간격을 늘릴 수 있다는 측면에서 편리하게 복용 가능하다는 결론을 도출하였다.

주요어: 타달라필, 포스포디에스테라아제 5형 억제제, 실데나필, 폐고혈압, 개

감사의 글

제주에서 학부 6년을 마치고, 벌써 어느덧 2년이라는 시간이 흘러 석사과정을 마치며 학위논문을 제출하게 되었습니다. 부족하지만 이 기회를 빌려 그동안 많은 도움을 주신 분들께 감사의 말씀을 전합니다.

학부 때부터 대학원까지, 학생으로 6년, 대학원생이자 수의사로 2년, 총 8년이라는 시간 동안 저를 올바른 인성과 역량을 갖춘 수의사로 나아갈 수 있도록 그 첫 걸음을 지도해주신 윤영민 교수님, 송우진 교수님께 존경과 감사의 말씀을 드립니다. 부족한 논문을 진심으로 지도해주시고 병원 진료에 크나큰 도움을 주신 김명철 교수님께도 감사의 말씀을 드립니다. 또한, 대학원 생활을 함께하며 서로 믿고 의지할 수 있는 버팀목이 되어준 동기 박종진, 김민건 선생님 그리고 내과실 선후배 분들, 파트 원장님들께도 감사의 말씀을 전합니다.

분임조 학생으로서 8년간 저를 따뜻한 마음으로 보살피고 아껴주신 정지열 교수님께 감사의 말씀을 드립니다. 또한, 임상/비임상 분야에서 진로를 고민하던 학부생 시절에 약리학실험실 및 로컬병원 실습 등 좋은 경험을 할 수 있도록 기회를 주시고 아낌없이 조언을 주신 주홍구 교수님을 비롯하여 로컬병원 원장님들, 그리고 필드에 나가 계신 모든 선배님께도 감사의 말씀을 드립니다. 긴 시간 타지에서 서로 의지하고 북돋아 주며 즐겁고 행복한 생활을 할 수 있도록 도움이 되어준 우리 제주대 16학번 동기들과 후배들에게도 감사의 인사를 전합니다.

학부생 때는 임상 로테이션 실습, 대학원생 때는 진료 수의사로서 부족한 저의 첫 직장이 되어준 제주대학교 동물병원의 동료 수의사분들과 모든 직원분께도 감사의 말씀을 드립니다.

무엇보다 타지에서 딸의 긴 학업 생활을 염려하고 격려해주신 부모님, 인생에서 항상 화목하고 든든한 버팀목이 되어주는 우리 가족과 반려묘 새울에게 무한한 감사와 사랑, 애틋함과 존경심을 담아 이 마음을 전합니다.

끝으로 부족한 저를 거쳐간 모든 생명들의 안녕을 빌며, 그 무게와 책임감을 항상 어깨에 짊어지고, 생명을 다루는 이 업에 있어 항상 신중하고 정진하는 수의사가 되겠습니다.

2024년 2월, 이새영 올림