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A retrospective study of 14 dogs with advanced heart failure treated with loop diuretics and hydrochlorothiazide

Koji Iwanaga[1], Ryuji Araki[1,2,3] and Mitsuhiro Isaka[3]*

[1]*Tokyo Veterinary Cardiology Center, Tokyo, Japan*
[2]*Yokohama Yamate Dog & Cat Medical Center, Kanagawaken, Japan*
[3]*Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan*

Abstract

Background: The use of thiazide diuretics is recommended in the American College of Veterinary Internal Medicine guidelines for advanced heart failure due to mitral insufficiency (MI) in dogs. However, there are no large-scale reports of the use of thiazide diuretics in dogs with advanced heart failure.

Aim: This retrospective study evaluated the therapeutic effect of concomitant hydrochlorothiazide (HTCZ) with loop diuretics in dogs with heart failure.

Methods: The study included 14 dogs diagnosed with advanced pulmonary edema with MI at two facilities. In all cases, high-dose loop diuretics (torsemide; 0.78–4 mg/kg/day) did not improve pulmonary edema. The results of the echocardiography and renal function tests before and after the administration of HTCZ (0.2–0.84 mg/kg/day) in addition to torsemide were statistically compared.

Results: The echocardiographic data demonstrated significant improvement in relation to cardiac stress; left atrium to the aorta ratio, normalized left ventricular internal dimension in diastole, and E wave velocity (*m/s*) after HTCZ administration. However, blood urea nitrogen and creatinine levels increased, and potassium levels decreased, indicating a decline in renal function following HTCZ administration.

Conclusion: This study suggests that the administration of HTCZ in combination with loop diuretics may be beneficial during advanced heart failure due to MI in dogs. The results can also be extended to patients who are resistant to loop diuretics, resulting in the improvement of cardiac function. However, as the combination of HTCZ and loop diuretics can deteriorate renal function, caution should be exercised prior to making recommendations regarding its use, and renal function should be monitored.

Keywords: Echocardiology, Hydrochlorothiazide, Loop diuretic, Mitral insufficiency, Pulmonary edema.

Introduction

Mitral insufficiency (MI) is the most common form of acquired heart disease in dogs, accounting for 75% of all cases in North America (Borgarelli and Haggstrom, 2010). Small dogs, such as the Cavalier King Charles Spaniel, are the most common breed, with most being small dogs being middle-aged. MI causes volume overload in the left heart system and manifests in the form of congestive left heart failure and pulmonary edema, causing respiratory distress (Borgarelli and Haggstrom, 2010). In severe cases, signs due to anterior output failure, such as exercise intolerance are also observed (Atkins and Häggström, 2012). Fainting attacks are sometimes seen and are deemed a poor prognostic factor (Borgarelli *et al*., 2008). In 2019, the American College of Veterinary Internal Medicine (ACVIM) published new guidelines for diagnosing and treating MI (Keene *et al*., 2019). The ACVIM guidelines recommend treatment with diuretics, mainly loop diuretics, after MI and Stage C severity. However, there are no large-scale reports on the use of thiazide diuretics in veterinary medicine, and the dose and effect determination is left to the veterinarian's judgment. Heart disease is on the rise with the increasing lifespan of dogs, and evidence related to its treatment with thiazide diuretics needs to be established. The concomitant use of thiazide and loop diuretics was previously reported in a human patient with heart disease who was resistant to treatment with loop diuretics (Jentzer *et al*., 2010). The long-term use of loop diuretics leads to the up-regulation of the thiazide-sensitive sodium ion transporter present in the distal tubules and hypertrophy of distal tubule cells. With loop diuretics alone, sodium ions, which have escaped reabsorption in the Loop of Henle, are reabsorbed in the distal tubules, which weaken the effect. Therefore, it has been reported in human medical treatment that to achieve a strong diuretic effect, the concomitant use of a thiazide diuretic inhibits the sodium6 chloride cotransport in distal tubules is required (Ellison, 1991; Sica and Gehr, 1996; Kim, 2004). This study

***Corresponding Author:** Mitsuhiro Isaka. Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan. Email: *m-isaka@rakuno.ac.jp*

evaluated the effect of a combination of thiazide and loop diuretics in dogs with heart failure due to MI that was unresponsive to high-dose loop diuretics alone. There are various thiazide diuretics, and in this study, hydrochlorothiazide (HTCZ) was used, which has been reported in human medicine (Robson *et al*., 1964; Dettli and Spring, 1966; Dormans and Gerlag, 1996; Vánky *et al*., 1997). The purpose of this study was to retrospectively evaluate the effects of using two drugs (HTCZ and loop diuretics) using echocardiography and renal function tests.

Material and Methods

Fourteen dogs were diagnosed with advanced pulmonary edema with MI at two facilities, Tokyo Veterinary Cardiology Center and Yokohama Yamate Dog and Cat Medical Center. The breeds of the cases were as follows: Chihuahua (n = 6), Boston Terrier (n = 1), Pomeranian (n = 1), Cavalier King Charles Spaniel (n = 1), Cockapoo (n = 1), Shih Tzu (n = 1), Toy Poodle (n = 2), and Miniature Schnauzer (n = 1). The mean body weight and age were 4.9 ± 2.2 kg and 132 ± 22 months, respectively. Physical examinations, chest X-rays, and echocardiography were mainly used for the diagnosis. LOGIC e9 (GE Health care Japan) (probe: 6S) was used at Tokyo Veterinary Cardiology Center for the echocardiography and Xario (TOSHIBA) (probe: PST-50AT) was used at Yokohama Yamate Dog and Cat Medical Center. All cases presented with severe MI, and the radiographic examination confirmed hyper-permeability of the lung field. As a result, all 14 dogs were diagnosed with cardiogenic pulmonary edema. In all cases, high-dose loop diuretics did not ameliorate pulmonary edema, and as such, the dogs were classified as having advanced pulmonary edema. Detailed information on the cases is summarized in Table 1. High doses of torsemide (1.49 ± 0.81 mg/kg/day), angiotensin-converting-enzyme inhibitor (1.19 ± 0.56 mg/kg/day), and pimobendan (0.97 ± 0.32 mg/kg/day) were used in all the cases. The amounts of torsemide and HTCZ are also shown in Table 2. Torsemide was administered in a wide range (0.78–4 mg/kg/day) as the renal side effects varied based on the patient. The results of the echocardiography and renal function tests before and after the administration of HTCZ were compared. Statistical differences between the two groups were compared using Welch's t-test. A p value < 0.05 was considered to be statistically significant.

Results and Discussion

The echocardiographic data showing cardiac stress improved significantly following the administration of HTCZ. The left atrium to the aorta ratio (LA/Ao) decreased from 3.18 ± 0.5 to 2.97 ± 0.55, normalized left ventricular internal dimension in diastole (LVIDDN) decreased from 2.23 ± 0.22 to 2.15 ± 0.33, and E wave velocity decreased from 1.7 ± 0.2 *m/s* to 1.5 ± 0.1 *m/s* following HTCZ administration. Furthermore, heart rate also improved (data not shown). As shown in Tables 3 and 4, a decline in renal function was observed with the following metrics following HTCZ administration: blood urea nitrogen increased from 41.3 ± 17.3 mg/dl to 75.8 ± 38.5 mg/dl, creatinine increased from 1.1 ± 0.4 mg/dl to 1.9 ± 1.2 mg/dl, and potassium ions decreased from 3.78 ± 0.48 mEq/l to 3.33 ± 0.33 mEq/l.

Grade classification and treatment methods are described in the ACVIMclassification for MI (Keene *et al*., 2019). Although loop diuretics such as furosemide and torsemide are often used in treating MI after Stage C, some patients with heart failure are resistant to treatment with loop diuretics. Patients with refractory heart failure are classified as Stage D according to the ACVIM classification, and the use of thiazide diuretics is considered for these patients (Keene *et al*., 2019). In human medical treatment, resistance to loop diuretics has been reported, and concomitant use of thiazide diuretics is recommended in such cases (Vánky *et al*., 1997). However, there is no report summarizing the treatment effects of HTCZ in combination with loop diuretics in heart failure due to MI in dogs. This study investigated 14 cases in which a combination of HTCZ and loop diuretics was used to treat heart failure due to MI. The dogs had been previously treated with loop diuretics; however, they did not respond to the treatment. The criteria for resistance to loop diuretics in this study were assessed based on the following criteria: no reduction in cardiac load and no change in renal function even though the loop diuretics were administered at the maximum doses. Several pathological conditions in which the effects of loop diuretics are diminished in humans have been reported. It has been reported that the renin-angiotensin-aldosterone system and sympathetic nervous system are enhanced in cases of high sodium intake, intestinal malabsorption, non-steroidal anti-inflammatory use, hypoalbuminemia, and in cases where sodium reabsorption is promoted in the distal nephrons (Jentzer *et al*., 2010). Although the echocardiography results improved significantly following the administration of HTCZ, a marked decline in renal function was also observed. It was suggested that the combination therapy of low-dose thiazide diuretics effectively improves heart failure resistance to loop diuretics. There is no previous report on the use of HTCZ in MI-induced heart failure in dogs. Although loop diuretic resistance is a condition encountered in human medicine, loop diuretic resistance should also be considered in dogs if high doses do not produce a marked effect.

This study has some limitations. First, renal function was measured by blood tests. If possible, urine volume and urine-specific gravity should also be measured to further understand the effects of a combination of HTCZ and loop diuretics on renal function. Second, this study had a small sample size. Further studies must include a higher number of cases. However, this study suggests that the administration of HTCZ is beneficial

Table 1. Case data, and type and dose of diuretics.

No	Breed	Age (month)	Body weight (kg)	Sex	Type of loop diuretics	DOSE of loop diuretics (mg/kg/day)	Type of thiazide	DOSE of thiazide (mg/kg/day)
1	Chihuahua	132	2.6	F	Torsemide	4	HTCZ	0.2
2	Chihuahua	108	2.3	S	Torsemide	1.74	HTCZ	0.68
3	Chihuahua	120	2.9	C	Torsemide	0.92	HTCZ	0.72
4	Chihuahua	177	4.9	C	Torsemide	1.22	HTCZ	0.38
5	Chihuahua	110	1.9	F	Torsemide	1.04	HTCZ	0.82
6	Chihuahua	120	2.9	M	Torsemide	1.38	HTCZ	0.72
7	Pomeranian	141	4.2	M	Torsemide	2	HTCZ	0.5
8	Shih Tzu	132	7.4	C	Torsemide	1.08	HTCZ	0.42
9	toy poodle	148	4.2	S	Torsemide	1.44	HTCZ	0.84
10	toy poodle	156	5.1	S	Torsemide	0.78	HTCZ	0.58
11	Miniature schnauzer	160	6.6	S	Torsemide	1.8	HTCZ	0.62
12	Boston Terrier	116	8.1	C	Torsemide	1.0	HTCZ	0.4
13	Cavalier King Charles Spaniel	91	7.4	C	Torsemide	1.08	HTCZ	0.42
14	Cockapoo	138	8.8	M	Torsemide	1.36	HTCZ	0.46
average		132 ± 22	4.9 ± 2.2			1.49 ± 0.81		0.55 ± 0.19

HTCZ = hydrochlorothiazide.

Table 2. Type and dose of angiotensin-converting enzyme inhibitors and pimobendane in all cases.

Case	Type of ACI	DOSE of ACI (mg/kg/day)	DOSE of pimobendan (mg/kg/day)
1	Temocapril hydrochloride	1.0	0.5
2	Benazepril hydrochloride	1.2	0.6
3	Benazepril hydrochloride	1.76	1.32
4	Benazepril hydrochloride	1.02	1.02
5	Enalapril hydrochloride	1.0	1.3
6	Alacepril hydrochloride	2.8	1.28
7	Enalapril hydrochloride	1.2	0.6
8	Benazepril hydrochloride	1.04	1.0
9	Benazepril hydrochloride	1.18	1.18
10	Unknown	Unknown	0.99
11	Benazepril hydrochloride	0.78	1.5
12	Enalapril hydrochloride	0.74	0.74
13	Benazepril hydrochloride	0.66	0.66
14	Benazepril hydrochloride	1.12	0.84

Table 3. Echocardiographic parameters before and after HTCZ administration.

Parameter	Before	After	*p* values
LA/Ao	3.18 ± 0.5	2.97± 0.55	<0.05
LVIDDN	2.23 ± 0.22	2.15 ± 0.33	<0.05
E velocity (*m/s*)	1.73 ± 0.21	1.51 ± 0.11	<0.05

LA = left atrial; LVIDD = left ventricular internal dimension in diastole; Ao = aortic root; LVIDDN = normalized left ventricular internal dimension in diastole.

Table 4. Renal function parameters before and after HTCZ administration.

Parameter	Before	After	*p* value
BUN (mg/dl)	41.3 ± 17.3	75.8 ± 38.5	<0.05
Creatinine (mg/dl)	1.1 ± 0.4	1.9 ± 1.2	<0.05
Na^{2+} (mEq/l)	141.4 ± 6.3	140.1 ± 5.8	0.3
K^{+} (mEq/l)	3.8 ± 0.5	3.3 ± 0.3	<0.05
Cl^{-} (mEq/l)	102.6 ± 8.0	100.1 ± 8.9	0.5

BUN = blood urea nitrogen.

in advanced heart failure due to MI in dogs and may be further applied to patients who are resistant to loop diuretics.

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Author contributions

Dr. Koji Iwanaga and Dr. Ryuji Araki collected data and prepared the manuscript. Dr. Isaka and approved the final version.

Conflict of interest

The authors declare that there is no conflict of interest.

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