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<Case Report>

Application of torsemide to two dogs with congestive heart failure

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Abstract : An 11-year-old castrated male Maltese weighing 3.6 kg and a 12-year-old intact female Shih-tzu weighing 6.5 kg were admitted to the Veterinary Medical Teaching Hospital of Chungnam National University with decompensatory congestive heart failure. Diuretic resistance was suspected due to long term diuretic therapy with furosemide. However, the patients improved after the furosemide treatment was changed to torsemide, demonstrating the benefits of application of torsemide to treat diuretic resistance caused by long term use of furosemide. These findings suggest that torsemide should be applied for treatment of diuretic resistance caused by long term use of furosemide.

Keywords : congestive heart failure, diuretic resistance, pulmonary edema, torsemide

Congestive heart failure (CHF) occurs when the heart is unable to provide sufficient pump action to maintain blood flow around the body [9]. As a result, the retention of fluid in tissue or body cavities can occur [9]. Loop diuretics are essential in the treatment of CHF in human and veterinary patients, because they reduce diastolic intraventricular pressure and capillary pressure, and the clinical signs associated with CHF including pulmonary edema, pleural effusion and ascites [10]. Furosemide and torsemide are loop diuretics commonly used in humans [6]. In contrast with furosemide, torsemide is not commonly used in veterinary medicine currently.

The efficacy of torsemide has been previously established in human patients with CHF [2]. According to a recent study in humans, cardiac mortality and hospital re-admission rate are reduced, and functional heart failure class was improved in patients treated with torsemide compared with furosemide or other diuretics [2]. These studies support the use of torsemide in veterinary medicine.

Torsemide is effective in patients with pulmonary edema caused by CHF at one-tenth of the furosemide dose [8]. Torsemide has a high bioavailability and a rapid absorption rate, even in patients with chronic renal failure, while the bioavailability and absorption rate of furosemide are reduced pathological states such as CHF [15]. Moreover, torsemide has a longer duration of diuretic action than furosemide, and also functions as an antagonist to aldosterone to competitively inhibit aldosterone-receptor binding in tubular cells [11, 12]. Because of this, torsemide, like spironolactone can inhibit myocardial remodeling and improve left ventricular function in CHF [1, 5].

In this case series, torsemide was used as a replacement for furosemide in the animals with suspected diuretic resistnace.

In first case, an 11-year-old castrated male Maltese dog, weighing 3.6 kg with a history of mitral valve insufficiency (MVI) and pulmonary edema, was referred with a chief complaint of cough, and labored breath. The patient had received management for heart failure 5 months previously. On physical examination, a holosystolic murmur (grade 5/6) was auscultated, and increased heart rate (210/min), respiratory rate (120/min) and blood pressure (173 mmHg) were found. Blood urea nitrogen (BUN) was increased to 29.7 mg/dL (reference range: 6.8~29.6) and electrolytes were within the normal range. Thoracic radiography showed severe left atrial bulging, a vertebral heart score of 12.0 and elevation of the tracheal bifurcation. Echocardiography showed eccentric hypertrophy, systolic dysfunction, severe MVI and severe pulmonary hypertension with fractional shortening (FS) of 46%, a left atrium (LA)/Aorta (Ao) ratio of 3.0, a regurgitant fraction (RF) of 72% and a pulmonary artery (PA) pressure of 75 mmHg. Integration of these results, it is assessed at left and right-sided congestive heart failure American College of Veterinary Internal Medicine (ACVIM) classification staging C.

On the basis of this assessment, the patient was prescribed furosemide (2 mg/kg q12 h, per os, Lasix; Handok Pharma, Korea), spironolactone (1.0 mg/kg q12 h, per os; Guju Pharma, Korea), pimobendan (0.3 mg/kg q12 h, per os, Vetmedin; Boehringer Ingelheim, Germany), theophylline (10 mg/kg q12 h, per os, Unifil tab. 200 mg; Mundi Pharma, Korea), ranitidine (1.0 mg/kg q12 h, per os, Ranitac; Hana Pharma, Korea),

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irbersartan (5.0 mg/kg q12 h, per os, Apurtan; Dong-a Pharma, Korea) and sildenafil (1.5 mg/kg q12 h, per os, Viagra tab. 50 mg; Pfizer, Korea).

After 3 months of this treatment, recurrent pulmonary edema occurred. The furosemide dose was then increased from 2.0 mg/kg q12 h to 2.5 mg/kg q12 h for one month, and the medication interval was shortened to three times a day. However, pulmonary edema was observed in this patient by thoracic radiography. In this situation, we prescribed torsemide instead of furosemide. The torsemide dose was 0.25 mg/kg q12 h, which is approximately one-tenth of the previous furosemide dose [7]. After prescription of torsemide, the clinical signs improved and were well maintained for 5 months.

In second case, a 12-year-old intact female Shih-tzu, weighing 6.5 kg was referred with the chief complaint of exercise intolerance, anorexia and a cough. Two years ago, the patient had been prescribed medication for heart failure at a local animal hospital in Japan. On physical examination, grade 4 holosystolic murmur was detected. All blood panels were within the normal range. Thoracic radiography showed mild tracheal elevation and echocardiography showed pulmonary hypertension, mitral and tricuspid valve regurgitation with FS 79.4%, LA/Ao ratio 1.7, RF 60.9% and PA 40 mmHg. Compared with severe valve degeneration, cardiac remodeling had scarcely progressed. Integration of these results led to an assessment of left-sided congestive heart failure ACVIM classification staging C.

On the basis of this assessment, the patient was prescribed furosemide at 2 mg/kg q12 h, theophylline at 10 mg/kg q12 h, famotidine at 0.5 mg/kg q12 h, irbersartan at 5.0 mg/kg q12 h, spironolactone at 1 mg/kg q12 h, and sildenafil at 1 mg/kg q12 h. After 6 months, the patient was hospitalized with recurrent pulmonary edema. On thoracic radiography, the interstitial pattern on the right caudal lung lobe was observed as being more severe than at the previous assessment (Fig. 1). The patient was prescribed furosemide at a constant rate infusion, a nitroglycerine patch (Angiderm patch 0.2 mg/h, Handok Pharma, Korea) and oxygen supply for recurrent pulmonary edema for 2 days. Echocardiography was also performed, and revealed more severe cardiac remodeling than had previously been observed. Hydrochlorothiazide (2 mg/kg q12 h per os, Dichlozid, Yu-han Pharma, Korea,) was added for the next 2 days. The following day, however, electrolyte abnormalities, such as hyponatremia, and hypokalemia, had worsened. We suspected that the electrolyte abnormalities might be from hypertrophy of the distal convoluted tubular cells caused by longstanding medication of loop diuretics medication. We changed the furosemide prescription with thiazide to torsemide 0.3 mg/kg q12 h. After the application of torsemide, the clinical signs including pulmonary edema were improved to within the normal range of electrolytes. This had been maintained for the past 5 months (Fig. 1).

Fluid accumulation producing edematous states is a common problem encountered in patients with CHF [9], thus it is important to reduce fluid overload with diuretic management. CHF increasingly requires higher doses of diuretics to alleviate clinical signs such as congestion. Typically as dogs receive higher doses of furosemide, they suffer more adverse effects, including electrolyte abnormalities, weakness and gastrointestinal disturbances. The decreasing diuretic effect of chronic furosemide usage is defined as diuretic resistance [7]. Recent experimental work has indicated ways in which the kidney adapts to chronic diuretic treatment and has indicated how these adaptations may limit diuretic effectiveness [9]. CHF represents the most common clinical situation in which diuretic resistance is observed. In mild CHF, diuretic resistance is not commonly encountered, as long as renal function is preserved. However, in moderate and severe CHF patients, diuretic resistance occurs more frequently and often becomes a clinical problem [3, 14].

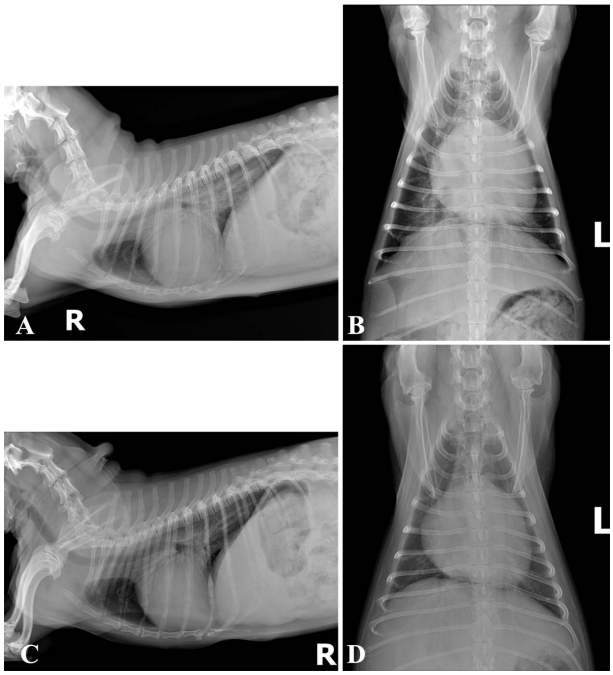

Fig. 1. Thoracic radiographs on furosemide administration period (A and B) and torsemide administration period (C and D), Compared with A and B, interstitial pattern was decreased at right caudal lung field in C and D.

In this case series, we described 2 dogs with CHF that were treated with a combination of cardiac medications and aggressive diuretic therapy with furosemide. In patients with CHF, diuretic dose must continually increase according to the disease progression, due to worsening fluid retention and diuretic resistance induced by decreased plasma blood flow and impaired secretion by the proximal tubule. These symptoms caused by low cardiac output, activation of the renin-angiotensin-aldosterone system, and vasoconstriction [3, 4]. The increase in diuretic action in this condition, it is indicated by increasing diuretic dose, shortening interval time and/or multiple diuretic combinations [3, 4]. The replace-

ment of furosemide with torsemide was also referred to in a recent study [7]. In this case series, we selected the application of torsemide as a replacement for furosemide to diminish the fluid accumulation caused by CHF, and found that it mitigates clinical sign such as pulmonary edema for a long period of time. Although the expected effects of loop diuretics, including hyponatremia, hypokalemia, hypochloremia, decreased urine specific gravity, and increased BUN and creatinine were observed [13], the quality of life for patients with CHF is also maintained well in these cases. The combination of furosemide and hydrochlorothiazide appears to be effective at combating refractory pulmonary edema, although clinicians must be aware of electrolyte abnormalities including hypokalemia [10]. In our second case, hyponatremia and hypokalemia worsened after the same combination of drugs. Therefore we prescribed torsemide instead of the combination of loop and thiazide diuretics.

Torsemide, like furosemide inhibits Na^+ and Cl^- reabsorption in the ascending loop of Henle via interference with the Cl^--binding site of the Na^+-K^+-$2Cl^-$ cotransport system [13]. Torsemide has a greater and more regular bioavailability, longer half-life, and longer duration of action than furosemide. The bioavailability of torsemide is about 80~100% compared to 10~100% for furosemide, its half-life after oral administration is about 8 h, which is longer than furosemide, and its duration of action is approximately twice that of furosemide (12 h *vs*. 6 h). In dogs with congestive heart failure, to produce diuresis and urinary sodium excretion equivalent to that in humans, the torsemide dose is 1/10 the dose of furosemide, whereas increased potassium excretion is less common [13]. We applied torsemide (0.3 mg/kg q12 h) at a 1/10 of the dose of furosemide in the present study. The clinical signs improved well and the electrolyte levels were within the normal range after application of torsemide. This was maintained over 5 months.

Consequently, its diuretic action is greater than furosemide and have fewer side effects have been observed [13]. Moreover torsemide is superior to furosemide in its anti-fibrotic effects on the myocardium as well as its blunting of loop diuretic resistance, which is mediated by torsemide's antagonism of aldosterone in a manner similar to that of spironolactone [1, 5]. For such reasons, torsemide is able to blunt diuretic resistance and lead to good progress. In one previous case report on the application of torsemide in patients with heart failure, all three cases did well and episodes of CHF were rare [7]. In another case report the diuretic effect of torsemide was found to be equal to or greater than furosemide, and urine potassium secretion was lower [13].

In this case series, the patients suffered from pulmonary edema caused by diuretic resistance. We applied increasing doses (per day) of furosemide and/or a combination of additional thiazide diuretics with furosemide to blunt diuretic resistance, but adverse effects such as electrolyte abnormalities occurred and clinical signs were not alleviated. We then decided to substitute torsemide for furosemide, and clinical improvement was observed. They patients remained in a good condition 5 month after replacement of furosemide with torsemide.

In conclusion, we applied torsemide as a substitution for furosemide in CHF patients with diuretic resistance suspected to be due to long term administration of furosemide in patients. The clinical signs of patients were improved after replacing furosemide with torsemide. The application of torsemide is therefore recommended for patients with diuretic resistance caused by long term use of furosemide.

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