Journal of Veterinary Cardiology (2012) 14, 253—259

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Journal of Veterinary Cardiology
ESVC

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Effect of torsemide and furosemide on clinical, laboratory, radiographic and quality of life variables in dogs with heart failure secondary to mitral valve disease

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Received 6 September 2011; received in revised form 29 December 2011; accepted 2 January 2012

KEYWORDS
Loop diuretic;
Mitral valve disease;
Aldosterone;
Diuretic resistance

Abstract *Objectives:* Diuretic therapy reduces preload and relieves congestion secondary to cardiac dysfunction. Torsemide (torasemide) is a loop diuretic with longer duration of action, decreased susceptibility to diuretic resistance, and adjunctive aldosterone antagonist properties compared with furosemide. We hypothesized that torsemide would be well tolerated and no less effective than furosemide at diuresis, control of clinical signs, and maintenance of quality of life (QOL) in dogs with congestive heart failure (CHF).
Animals, materials and methods: Seven client-owned dogs with stable CHF receiving twice daily oral furosemide and adjunctive medications. Utilizing a double-blinded, randomized, crossover design, dogs were administered either oral furosemide at their current dose or an equivalent oral dose of torsemide (1/10 of the daily furosemide dose divided into twice daily dosing) on day 0. Crossover occurred at day 7 and the study ended on day 14. Clinical, laboratory, radiographic, and QOL variables were evaluated on days 0, 7 and 14.
Results: No dogs developed recurrent CHF during the study. Mean furosemide dose on day 0 was 5.13 mg/kg/day (range 2.8—9.6). Following torsemide treatment, creatinine ($P = 0.020$), urea nitrogen ($P = 0.013$), phosphorus ($P = 0.032$), albumin

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1760-2734/$ - see front matter
doi:10.1016/j.jvc.2012.01.003

($P = 0.019$), carbon dioxide ($P = 0.015$) and anion gap ($P = 0.005$) were significantly increased, and urine specific gravity ($P = 0.004$) and chloride ($P = 0.021$) were significantly decreased compared with furosemide dosing. No differences in QOL were found.
Conclusions: Results indicate that torsemide is equivalent to furosemide at controlling clinical signs of CHF in dogs and is likely to achieve greater diuresis vs. furosemide. Larger clinical trials evaluating torsemide as a first or second-line loop diuretic for congestive heart failure in dogs are warranted.

Abbreviations

ACEI	angiotensin-converting enzyme inhibitors
BUN	blood urea nitrogen
CHF	congestive heart failure
FETCH	Functional Evaluation of Cardiac Health
QOL	quality of life
USG	urine specific gravity

Introduction

Loop diuretics are a mainstay of treatment for CHF in human and veterinary patients because of their ability to reduce intravascular hydrostatic pressure and reduce the clinical signs associated with edema formation.[1,2] Furosemide[b] and torsemide[c] (torasemide) are loop diuretics commonly used in humans.[3] While furosemide is commonly used in veterinary patients with CHF, the use of torsemide in veterinary medicine is not well described. Torsemide (1-isopropyl-3[(4-m-toluidino-3-pyridyl) sulphonyl]urea) is a pyridyl sulfonylurea with a chemical structure between that of traditional loop diuretics and Cl- channel blockers.[4,5] Its primary site of action is the thick ascending loop of Henle in the nephron, where it promotes excretion of sodium, water, and chloride via interaction with the Na^+, K^+, $2Cl^-$ cotransporter.[4,6,7] In humans, torsemide has a higher bioavailability, longer half-life, and longer duration of action than furosemide, resulting in a more uniform action of diuresis that is both stronger and more effective.[8,9]

Torsemide's safety and efficacy are well established in human patients with CHF. A recent review cited evidence that torsemide has more favorable pharmacokinetics, efficacy, and safety than furosemide in patients with heart failure and recommended that torsemide be considered a first-line therapy in humans with heart failure.[10] The TORIC study (Torasemide in Congestive Heart Failure) demonstrated a significantly lower total mortality/cardiac mortality, greater improvement in New York Heart Association (NYHA) functional heart failure class and reduction in hospital readmission rate in human patients treated with torsemide (compared with furosemide and other diuretics).[9] These findings have been duplicated in subsequent studies.[3,8] Torsemide's superiority over furosemide is likely due to antifibrotic effects on the myocardium as well as blunting of loop diuretic resistance, effects that appear mediated by torsemide's antagonism of aldosterone in a manner similar to that of spironolactone[d].[11,12] Addition of spironolactone to treatment regimens in human CHF patients significantly reduces mortality and a recent study in dogs supports improved survival in dogs with ISACHC class II and III degenerative mitral valve disease with spironolactone therapy.[13,14] Torsemide also improves cardiac sympathetic nerve activity and decreases plasma brain natriuretic peptide (BNP) levels in humans with CHF. These parameters have been demonstrated to be strong prognostic indicators for survival in humans with CHF.[15]

Limited data exists on the use of torsemide as a diuretic or in treatment of CHF in dogs and its effects on laboratory parameters and clinical signs have not been directly compared with furosemide. A small study in a group of dogs with CHF secondary to degenerative mitral valve disease evaluated serum and urine electrolytes during short-term use of

[b] Lasix, Sanofi-Aventis U.S. LLC, Bridgewater, NJ.
[c] Demadex, Meda Pharmaceuticals Inc., Somerset, NJ.
[d] Aldactone, Pfizer Inc, New York, NY.

torsemide and an angiotensin-converting enzyme inhibitor (ACEI) compared with an ACEI alone. Results indicated a significant decrease in serum chloride when receiving both drugs.[16] In healthy dogs, the dose of torsemide needed to achieve equivalent diuresis is one-tenth (1/10) the dose of furosemide.[4] The duration of action of oral torsemide (12 h) in dogs is longer than that of furosemide (6 h).[4,17]

The main objective of this study was to evaluate the comparative effects of torsemide and furosemide on serial clinical, laboratory, radiographic, and owner-perceived quality of life (QOL) variables in dogs with clinically stable CHF secondary to naturally occurring degenerative mitral valve disease that were already receiving furosemide therapy. We hypothesized that torsemide would be well tolerated and no less effective than furosemide with regards to control of clinical signs, degree of diuresis based on laboratory values, and QOL in this population of dogs.

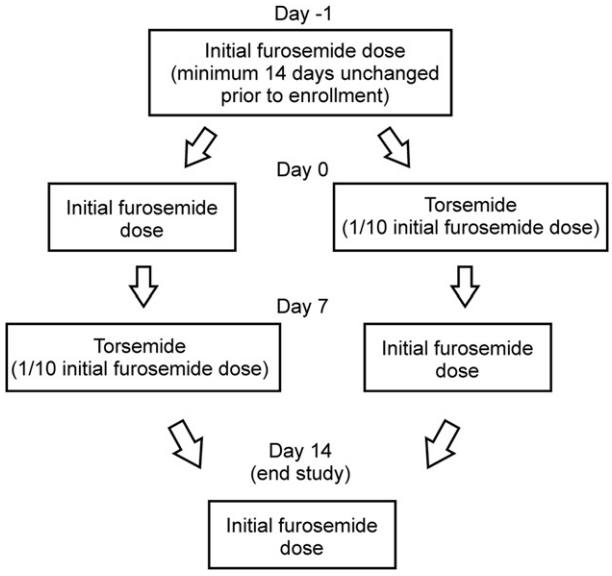

Figure 1 Flow diagram illustrating study design for a prospective, double-blinded, randomized, crossover study comparing torsemide with furosemide in dogs with clinically stable congestive heart failure. Data was collected at days 0, 7, and 14.

Animals, materials and methods

Study population

Seven dogs with clinically stable left sided CHF (modified ACC/AHA heart failure class C) secondary to naturally occurring degenerative mitral valve disease were enrolled in the study.[18] All dogs were receiving static twice daily PO furosemide for at least 14 days prior to enrollment. Concurrent therapy with adjunctive cardiopulmonary medications (such as ACEI and pimobendan) was permitted provided the doses of these medications had not been adjusted within the 7 day period prior to enrollment. All dogs had previously received a standard echocardiogram[e] to confirm the diagnosis of degenerative mitral valve disease. Dogs were excluded if they had significant concurrent cardiac or extra-cardiac disease (including renal disease) based on the opinion of the attending cardiologist.

Study design

The study was designed as a prospective, double-blinded, randomized, crossover study. Dogs were enrolled at day zero and randomly assigned to continue receiving their existing twice daily PO furosemide dose or an equivalent dose of PO torsemide (calculated as 1/10 the daily furosemide dose divided BID) in addition to their adjunctive medications. Crossover occurred on day 7 and the study ended on day 14 (Fig. 1). The primary endpoint for the study was recurrence of congestive heart failure (defined as clinical dyspnea, tachypnea, or coughing in direct association with radiographic cardiomegaly, pulmonary venous congestion, and pulmonary edema). Secondary endpoints included urine specific gravity (USG), serum blood urea nitrogen (BUN) and creatinine, blood pressure, and owner-perceived QOL. Clinical, laboratory, radiographic, and QOL variables were evaluated on days zero, seven and 14. All variables were evaluated between 9 am and 4 pm. Differences in owner availability resulted in some variability among dogs with regard to what time of day these visits occurred. For each individual dog, however, variables were assessed at the same time of day for each of the three different visits. Each dog was evaluated by the same clinician on all three visits.

Clinical variables

Objective physical examination variables evaluated included body weight (kilograms), resting heart rate (beats per minute), and respirations per minute.

Laboratory variables

Laboratory variables obtained at each visit included Doppler[f] systolic blood pressure (mm Hg),

[e] Philips Sonos 7500, Philips Medical Systems, Bothell, WA.

[f] SAS version 9.3, SAS Institute, Cary NC.

USG (urine obtained via free catch), and serum renal chemistry analysis including BUN (mg/dl), creatinine (mg/dl), BUN/creatinine ratio, phosphorus (mg/dl), calcium (mg/dl), sodium (mmol/L), potassium (mmol/L), chloride (mmol/L), carbon dioxide (mmol/L), albumin (g/dl), and anion gap (mmol/L). Blood samples were obtained via jugular, cephalic, or saphenous venipuncture.

Radiographic variables

Right lateral and ventrodorsal thoracic radiographs were obtained at each visit for all dogs. Thoracic radiographs were evaluated by a board-certified cardiologist (MAO) blinded to the patient's treatment assignment. A vertebral heart scale (VHS) was used to objectively assess heart size.[19] The determination of whether active congestive heart failure was present was based on the combination of left sided heart enlargement, pulmonary venous distension, and a moderate-severe interstitial and/or alveolar pulmonary parenchymal pattern consistent with pulmonary edema. Cranial lobar pulmonary vein size was determined and graded according to the following scale: 0 — normal size, 1 — mild distension, 2 — moderate distension, 3 — severe distension. A pulmonary parenchymal density score was determined and graded according to the following scale: 0 — normal lung fields, 1 — mild interstitial pattern, 2 — moderate interstitial pattern, 3 — severe interstitial-alveolar pattern.

Quality of life variables

Owner-perceived quality of life was assessed at each visit by completion of a Functional Evaluation of Cardiac Health (FETCH) questionnaire by the owner.[20] After completing each FETCH questionnaire owners were invited to separately record their subjective impression of any additional clinical side effects or changes in their pet's condition noted during the week. By design of the study, owner and investigators remained blinded to the patient's treatment assignment at the time these comments were recorded.

Statistical analysis

An ANCOVA appropriate for a two period crossover design with 2 treatment groups was used to analyze the data using the MIXED procedure in a statistical software package.[g] The model included treatment sequence, study period and treatment as fixed effects. Dog within sequence was used to evaluate the sequence effects. Study period was evaluated as a repeated measure. Outcomes were deemed to be statistically significant if $P < 0.05$. Baseline values (Day 0) were included as a covariate.

[g] SAS version 9.3, SAS Institute, Cary NC.

Results

Breeds of dog represented in the study included one each of the following: Miniature Dachshund, Miniature Poodle, Toy Poodle, Whippet, American Pit Bull Terrier, Cavalier King Charles Spaniel, and Pomeranian. Mean body weight at the time of enrollment was 10.8 kg (range: 4.5—26.8). Mean furosemide dose at the time of enrollment was 5.13 mg/kg/day (range: 2.8—9.6). Other medications at the time of enrollment and throughout the study period included enalapril (6 dogs), pimobendan (5), aldactazide (hydrochlorothiazide + spironolactone) (2), spironolactone (2), benazepril (1), digoxin (1), hydrocodone (1) and extended-release theophylline (1). Following unblinding, three dogs had received torsemide during days 0—7 and four dogs had received torsemide during days 7—14.

All dogs completed the study. None of the dogs developed clinical or radiographic congestive heart failure during the study. Results of clinical, radiographic, laboratory, and QOL variables during furosemide vs. torsemide treatment are listed in Table 1. Small but significant increases in creatinine, BUN, phosphorous, carbon dioxide, albumin, and anion gap were detected following torsemide treatment. Small but significant decreases in USG and chloride were detected following torsemide treatment. No other significant differences in laboratory or radiographic variables, physical examination parameters, or QOL scores were detected between groups (Table 1). The statistical analysis revealed no statistically significant sequence or period effects for any outcome ($P > .05$). Three subjective comments were recorded by owners during the study period. One owner reported that the dog seemed more tired and was having fewer urinary accidents in the house during the furosemide treatment period. Two owners reported an increase in frequency of urination by their dogs during the torsemide period.

Discussion

Results of this clinical trial indicate that torsemide was well tolerated and equally effective as furosemide at controlling clinical and radiographic

Table 1 Least squares mean and standard error of the mean (SEM) of clinical, radiographic, laboratory, and quality of life variables comparing furosemide (F) with torsemide (T) For treatment of congestive heart failure in dogs ($n = 7$ dogs).

Variable	F	F (SEM)	T	T (SEM)	*P* value
Body weight (kilograms)	10.57	0.269	10.39	0.269	0.111
Heart rate (beats/minute)	151	8.8	149	8.8	0.787
Respiratory rate (breaths/min)*	27	3.2	29	3.0	0.525
Doppler systolic blood pressure (mm Hg)	132	6.7	131	6.7	0.860
Urine specific gravity (USG)	1.013	0.001	1.010	0.001	0.004*
Blood urea nitrogen (BUN) (mg/dl)	30.1	5.19	43.8	5.19	0.013*
Creatinine (mg/dl)	0.85	0.097	1.08	0.097	0.020*
Phosphorus (mg/dl)	4.18	0.246	4.92	0.246	0.032*
Calcium (mg/dl)	10.42	0.210	10.55	0.210	0.640
Sodium (mmol/L)	141.8	1.29	141.1	1.29	0.725
Potassium (mmol/L)	4.33	0.105	4.32	0.105	0.932
Chloride (mmol/L)	107.2	1.69	101.8	1.69	0.021*
Carbon dioxide (mmol/L)	25.4	0.82	26.9	0.82	0.015*
Albumin (g/dl)	3.26	0.070	3.50	0.070	0.019*
Anion gap (mmol/L)	10.1	1.23	12.58	1.23	0.005*
Vertebral Heart Scale (v)	12.2	0.09	12.1	0.09	0.352
Pulmonary vein score (0–3)	0.32	0.208	0.40	0.208	0.721
Pulmonary density score (0–3)	0.40	0.099	0.57	0.099	0.286
FETCH QOL Value	16.0	2.14	16.3	2.14	0.918

*Indicates statistically significant difference. *$n = 5$, dogs with panting were excluded.

heart failure in the short-term in dogs with stable CHF secondary to degenerative mitral valve disease. The dose of torsemide that was used in this study was based on equivalence studies with furosemide in healthy dogs.[4,17] Expected direct effects of loop diuretics include hyponatremia, hypokalemia, hypochloremia, increased anion gap and decreased urine specific gravity, among others. Indirect effects of loop diuretics might include increased BUN, creatinine and phosphorus (via decreased effective circulating blood volume and renal blood flow ± renal tubular injury) and increased albumin (as a marker of reduced plasma volume). Expected direct effects of spironolactone include hyponatremia, hyperchloremia, hyperkalemia, and decreased urine specific gravity. Indirect effects would be similar to those seen with loop diuretics. The biochemical effects of a diuretic with actions of both of the above diuretic classes in addition to direct chloride channel blockade are expected to be complex and beyond the scope of this discussion. However, the overall serum chemistry and urinalysis findings in dogs in this study do suggest an increased degree of diuresis during the time period in which dogs were receiving torsemide therapy. The lack of any detectable change in sodium among groups despite changes in other electrolyte concentrations may be due to differences in the kidney's complex regulation of extracellular sodium compared with other electrolytes, particularly in the setting of elevated sympathetic nervous system activity present with heart failure. This disparity in electrolyte changes also suggests that the direct chloride channel blockade activity of tosemide may be the cause of these changes.

Greater overall diuresis with torsemide compared with furosemide may be linked to blunting of diuretic resistance via torsemide's aldosterone antagonist properties. Diuretic resistance with long-term furosemide use is a known phenomenon that occurs in part due to overexpression of renal electrolyte transporters, including the Na+-Cl- cotransporter, an aldosterone-induced protein.[12] This overexpression can be inhibited with aldosterone antagonist administration.[12] There is experimental evidence to support that torsemide interferes with the secretion of, and receptor ligand binding of, the mineralocorticoid aldosterone in a dose-dependent manner.[13,21,22] Torsemide results in elevated levels of circulating angiotensin II and aldosterone (supportive of interference with aldosterone at the receptor level) in dogs with experimental mitral regurgitation whereas furosemide results in elevated levels of angiotensin II, only.[4] A recent study in healthy dogs demonstrated persistent diuretic activity with long-term torsemide use compared with furosemide.[23]

No differences in FETCH-measured QOL between groups were identified in this study. In humans with CHF, torsemide improves patient quality of life compared with furosemide via

decreased urgency to urinate, decreased overall mictions, and decreased social activity restriction.[8] It is possible that these effects are not present or significant in dogs, or alternatively that the inherent difficulty in quantifying variables such as 'urgency to urinate' and 'social activity restriction' in veterinary patients may preclude detection of such differences. No adverse effects were noted during the study period in either group. Adverse effects of torsemide are uncommon in humans but include fatigue, weakness, hypotension, skin rash, electrocardiographic abnormalities (atrial fibrillation), gastrointestinal upset, and urine retention. The majority of these are related to volume and electrolyte changes and do not appear to occur with any greater frequency than that which occurs in patients treated with furosemide.[8]

Limitations of the study include the small number of dogs, requirement for some of the furosemide and/or torsemide tablets to be manually halved or quartered which made achieving precise dosage more difficult, and inter-dog variability with respect to the time of day of visits. We do note, however, that appropriate for this crossover study design, time of visit for any individual dog (i.e., intra-dog) across the three visits remained conserved. The short duration of the study period precludes any direct comparison of differences between the two drugs over a long-term treatment period and may have limited the ability to evaluate quality of life parameters. Since all dogs were on furosemide at baseline, evaluation of torsemide as a first-line diuretic compared with furosemide in dogs with CHF is not possible from this study. Furthermore, because the study population consisted entirely of dogs in clinical heart failure, it was not feasible to include a washout period between loop diuretics due to the risk of decompensation to the dogs that would have occurred with such a design. The statistical analysis method used in this study investigated for confounding effects of treatment sequence and study period on the results. No such effects were detected, however. Biochemical analysis of serum/urine neurohormone levels and urinary excretion profiles were not performed but might have allowed for further evaluation of the aldosterone antagonist properties of the two diuretics.

Conclusions

In our study population, torsemide was well tolerated and displayed similar short-term efficacy as furosemide at maintaining clinically stable heart failure in dogs with degenerative mitral valve disease previously receiving chronic furosemide therapy. Significant differences in blood and urine variables in this study population suggested torsemide achieved greater diuresis than doses of furosemide considered equivalent in healthy dogs. Results of this pilot study indicate that large-scale, longitudinal clinical trials comparing efficacy and long-term safety of torsemide vs. furosemide therapy in canine heart failure are warranted.

Funding

This study was supported by a Departmental Research Grant, Department of Clinical Studies-Philadelphia, Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania, 2009.

Conflict of interest

The authors have no conflict of interest.

Acknowledgments

The authors thank Carolyn Michel, CVT for her technical assistance in this project and Steven Radecki for statistical assistance.

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