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Long-term Stability of a Compounded Suspension of Torsemide (5 mg/mL) for Oral Administration

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Background: Torsemide use for congestive heart failure (CHF) has been reported, but prescription frequency is unknown. Commercially available tablet sizes in North America limit dosing precision, indicating a need to evaluate its strength and stability in suspension.

Objectives: To determine the frequency of torsemide prescriptions and to determine a beyond use date (BUD) of a compounded suspension of torsemide for oral administration stored under 2 temperature conditions for 90 days.

Animals: No animals used.

Methods: Pharmacy records were retrospectively reviewed for torsemide and furosemide prescriptions from 2008 to 2015 at 2 veterinary referral centers. After preliminary strength testing, compounded torsemide suspension (5 mg/mL) for oral administration was prepared using torsemide tablets suspended in OraPlus:OraSweet 1:1, buffered to a pH of 8.3 and stored at refrigeration (2–8°C) and room temperature (20–25°C) in 2 oz amber plastic bottles. Samples were analyzed by reverse phase high-performance liquid chromatography (RP-HPLC) on days 0, 14, 30, 60, and 90.

Results: Prescriptions for torsemide increased from 2008 to 2015. Analysis of the torsemide 5 mg/mL suspension for oral administration at each time point met United States Pharmacopeia (USP) requirements for torsemide content of 90–110% of label claim. The average strength at 90 days decreased to 92 ± 3% at 2–8°C and 95 ± 2% at 20–25°C. Stability testing did not detect unknown impurities.

Conclusions: Increasing torsemide use warrants availability of a validated and stable compounded formulation. Our results support the assignment of a 90-day BUD for torsemide 5 mg/mL suspension for oral administration compounded in OraPlus:Sweet 1:1 buffered to a pH of 8.3.

Key words: Heart failure; Loop diuretic.

Furosemide is the most commonly prescribed diuretic for congestive heart failure (CHF). Recently, torsemide has received attention because of greater potency, better bioavailability, longer duration of action and aldosterone antagonism.[1–6,a] Torsemide's diuretic efficacy is 10 times, and its duration of action is twice (12 hours) that of furosemide.[1,3,6] Several reports describe the use of torsemide to treat CHF in dogs and cats, demonstrating current use, and encouraging future use.[2,4,5,a]

Because of the greater potency of torsemide, the smallest tablet size available in North America (5 mg) can limit accurate dosing. Although all but the smallest patients can be dosed initially using fractions of the commercially available tablets, dose adjustments are challenging because the smallest change possible (1/4 tablet or 1.25 mg) is equivalent to a furosemide dose increase of 12.5 mg. For small dogs and cats, this amount of dose increase may be excessive and potentially could compromise hydration and renal function.

Compounding pharmacies have been used to formulate torsemide into a suspension for oral administration to facilitate lower doses and small dose changes[a], but the long-term strength and stability of torsemide suspension in any vehicle have not been reported. Strength is the concentration of a drug in a preparation, whereas stability is the extent to which a drug retains its original properties separate from degradation products and impurities. Stability-indicating methods also can determine strength, but not all strength determining methods indicate stability. Consequences of drug instability include subtherapeutic dosing due to strength loss and detrimental effects of degradation products.[7,8] Stability is especially important for medications used to treat cardiac disease, where administration is lifelong and deficient quality can lead to suffering or death.

Abbreviations:

BUD	beyond use date
CHF	congestive heart failure
MedVet	MedVet, Medical and Cancer Center for Pets
NCSU-CVM	North Carolina State University College of Veterinary Medicine
NF	National Formulary
RP-HPLC	reverse phase high-performance liquid chromatography
USP	United States Pharmacopeia

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Where Work was Performed: North Carolina State University, College of Veterinary Medicine, Raleigh, NC and Campbell University, Pharmaceutical Education & Research Center, College of Pharmacy & Health Sciences, Buies Creek, NC.

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Traditional compounding vehicle options include aqueous, oil, and glycerin liquids. The United States Pharmacopeia (USP) default beyond use date (BUD) of 14 days for water-containing liquids for oral use (eg, aqueous and glycerin vehicles) is impractical for medications requiring chronic administration.[b] Chronic oral administration of the vehicle glycerin USP also may not be ideal because of the potential for catharsis. The USP default BUD of 180 days for anhydrous (oil) liquids[b] for oral use is appealing, but aspiration of oils is a serious risk in animals with CHF. OraPlus®[c] is a commercially available aqueous-based suspending vehicle with a longer shelf life and acidic pH (4.2). When combined with OraSweet®[d] this vehicle has good palatability. The alkaline pH (8.3) of injectable torsemide solution[e] and the reported high percentage of forced degradation in acidic conditions (10.8%) as compared to basic conditions (0.4%) indicates that an alkaline pH of the vehicle is important to torsemide stability.[9]

One objective of our study was to retrospectively evaluate the number of torsemide prescriptions compared to furosemide prescriptions over 8 years at 2 veterinary referral centers. We hypothesized that later years would show an increase in torsemide prescriptions. We also sought to evaluate compounded torsemide 5 mg/mL suspensions for long-term strength and stability. We hypothesized that suspensions prepared in a buffered alkaline compounding vehicle would retain strength and stability over 90 days at cold refrigeration and room temperatures.

Methods

Retrospective Review of Diuretic Prescriptions

Pharmacy records were retrospectively evaluated to determine the number of dogs and cats that were prescribed furosemide and torsemide from 2008 to 2015 at 2 veterinary referral centers (North Carolina State University College of Veterinary Medicine, Raleigh, NC [NCSU-CVM] and MedVet, Medical and Cancer Center for Pets, Worthington, Cincinnati and Dayton sites, OH [MedVet]). Each diuretic prescription was recorded only once for each patient, when first prescribed (refills not recorded). Torsemide prescriptions were determined to be first-diuretic prescriptions if torsemide was the initial diuretic prescribed or second-diuretic prescriptions if torsemide was prescribed to replace a previous prescription for furosemide. The number of compounded torsemide prescriptions also was recorded.

Strength and Stability Testing of Compounded Torsemide

Preliminary Short-Term Strength Testing

A preliminary short-term strength determination of 3 separate vehicle suspensions of torsemide 5 mg/mL was assessed. The 3 suspensions, prepared by the NCSU-CVM Pharmacy, were non-buffered aqueous OraPlus®[c]:OraSweet®[d] (1:1 blend, pH 4.2); corn oil, National Formulary (NF); glycerin USP. Compounded torsemide 5 mg/mL was prepared by crushing 50 commercially available 10 mg torsemide tablets[e] (500 mg total) in a mortar with a pestle until a fine powder was obtained. The powder was mixed with the vehicle and transferred to a 100 mL calibrated beaker, rinsing the mortar several times with additional vehicle, and then bringing to final volume of 100 mL with additional vehicle. The contents were thoroughly mixed, then transferred into 2-oz amber, plastic, child-resistant, prescription bottles for triplicate strength testing at 2–8°C. Suspensions were shipped to an outside commercial laboratory[f] on ice the same day as preparation (day 0), and quantitative analysis of torsemide content was performed at days 0 and 7. Strength was considered acceptable if drug concentration (as expressed by percentage of the label claim) was >90%.

Reverse Phase High-Performance Liquid Chromatography (RP-HPLC)

In preparation for long-term strength and stability testing, a published RP-HPLC method for measuring torsemide concentrations was evaluated at Campbell University Pharmaceutical Education and Research Center.[9] This method not only determines drug strength but has been shown to separate impurities and degradants from active drug concentrations, an important feature of a stability-indicating assay.[9] The appropriateness of the chromatographic method conditions was evaluated by assessing the following method performance variables: Standard stress degradation, compounded preparation stress degradation, filter compatibility, linearity, specificity and accuracy, repeatability, range, and ruggedness.[9] Torsemide concentrations were expressed as a percentage of the label claim as a measure of strength, and stability was assessed by evaluating chromatograms at each time point under each temperature condition.

The conditions used for sample analysis were as follows: column: Phenomenex Luna C18(2) 50 × 3.0 mm, 3 microns, 100Å (parts number: 00B-4251- Y0; serial number: 778091-8), column temperature: 40°C, injection volume: 6 µL, flow rate: 1.0 mL/min, detector: ultraviolet (UV) absorbance at 288 nm; pump program: mobile phase B; 25–35% in 3.5 minutes, 35–75% to 4 minutes, hold 75% to 4.6 minutes, back to 25% at 5 minutes, hold 25% to 6 minutes, postrun at 25% for 2 minutes; mobile phase A; 90:10 (v/v) buffer:acetonitrile; mobile phase B – 50:50 (v/v); buffer:acetonitrile; buffer: 20 mM sodium monobasic phosphate at pH 3.6; sample phase diluent: 25:25:50 (v/v) buffer: acetonitrile: methanol.

Long-Term Strength and Stability Testing

Based on preliminary results, a torsemide 5 mg/mL suspension using OraPlus®[c]:OraSweet®[d] buffered to an alkaline pH as the vehicle was assessed for long-term strength and stability. Compounded torsemide 5 mg/mL was prepared by crushing 50 commercially available 10 mg torsemide tablets[e] (500 mg total) in a mortar with a pestle until a fine powder was obtained. A 1:1 blend of OraPlus[c]:OraSweet[d] was added to the drug powder and titrated in the mortar to obtain a pourable liquid. The contents of the mortar were transferred to a 100-mL calibrated beaker, rinsing the mortar several times with additional vehicle, then bringing to final volume of 100 mL with additional vehicle. Sodium hydroxide 2N[g] was added dropwise to achieve a final pH of 8.3. The contents were thoroughly mixed, and then transferred into 2-oz amber, plastic, child-resistant, prescription bottles for strength and stability testing. Three batches of 100 mL compounded torsemide 5 mg/mL suspension for oral use (Lot #1–3) were prepared to provide 6 aliquots for triplicate testing of storage at room temperature (20–25°C) and refrigeration (2–8°C). Transportation to Campbell University Pharmaceutical Education and Research Center (<1 hour) for strength and stability testing was carried out on the day of preparation, and aliquots intended for refrigeration were transported on ice. Strength and stability testing by RP-HPLC was performed at days 0, 14, 30, 60, and 90. The vehicle[c, d] and reference standard torsemide[e] also were evaluated by RP-HPLC to elucidate specific peaks related to these compounds in the sample preparations. The lower limit of quantification was 0.1 µg/mL

The USP requirement for stability was considered met if torsemide concentrations (expressed as the percentage of the label

claim) were between 90 and 110% of the initial concentration when stored at the controlled temperatures described. The time point before the average torsemide concentration decreased below 90% of the initial concentration was considered the BUD for each suspension.

Statistical Analysis

Strength values for each of the 3 lots of compounded torsemide suspension at each time point and under both storage conditions were expressed as mean ± standard deviation, and 95% confidence intervals (CI) were reported.

Results

Retrospective Review of Diuretic Prescriptions

There were 6,084 prescriptions for furosemide and torsemide at both referral centers during this time period. Figure 1 shows the absolute number and percentage of all the prescriptions that were for torsemide by year at NCSU-CVM and MedVet from 2008 to 2015 (only the initial prescription is presented, not refills). Although furosemide was the most commonly prescribed diuretic, an increase in torsemide prescriptions occurred over the 8 years reviewed. A total of 260 patients received torsemide at both centers, 52 of which were first-time diuretic prescriptions (torsemide was the first diuretic prescribed for CHF) and 208 of which were second-diuretic prescriptions (ie, the patient was switched from furosemide to torsemide). More cats received torsemide during this time period at MedVet (60) than at NCSU-CVM (1) and 30 of the 61 cats were prescribed compounded torsemide.

Strength and Stability Testing of Compounded Torsemide

Preliminary Short-Term Strength Testing

A preliminary strength determination of 3 separate solutions of torsemide 5 mg/mL prepared in non-buffered aqueous OraPlus®[c]:OraSweet®[d] (pH 4.2); corn oil, NF; glycerin, USP showed that torsemide prepared in these vehicles decreased in strength from 100% on day 0 to day 7 concentrations of 91% for OraPlus®[c]:OraSweet®[d], 90% for corn oil, NF and 93% for glycerin USP. Because of the rapid decrease in strength over only 7 days, these formulations were considered unsuitable for chronic use, and compounding modifications were pursued. OraPlus®[c]:OraSweet®[d] was considered the most appropriate suspending vehicle because it is aqueous (not oil based) and is not associated with gastrointestinal upset. Because previous studies have indicated significant torsemide degradation in acidic conditions,[9] long-term strength and stability testing were pursued with OraPlus®[c]:OraSweet®[d] buffered to an alkaline pH targeted to match that of injectable torsemide (pH 8.3).[h]

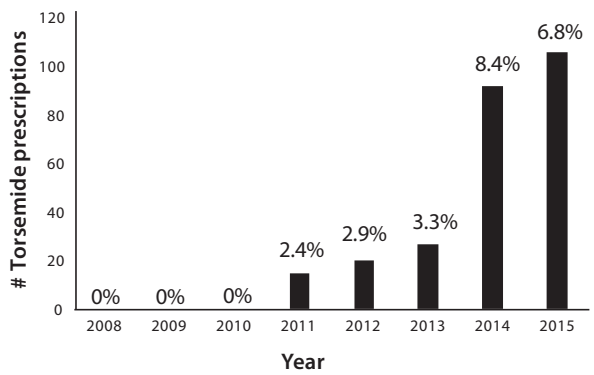

Fig 1. Number of prescriptions and percentage of total prescriptions that are torsemide prescriptions, by year at both centers (NCSU and MedVet) from 2008 to 2015.

Reverse Phase High-Performance Liquid Chromatography

The RP-HPLC method met the evaluation criteria for linearity. The linearity standard curve (Fig 2) showed high correlation between concentration and area under the curve using 4 dilutions. All data generated was relative to a USP reference standard of torsemide[e]. Example chromatograms for the reference standard as well as compounded torsemide suspension are shown in Figure 3 demonstrating that torsemide can be separated from other compounds and that unknown impurities were not detected. These chromatograms are representative of all time points at both storage conditions. The large peak at 2.47 minutes represents torsemide. The small peak at 0.85 minutes represents torsemide-related compound A, a known impurity present in the reference standard and suspensions. The 4 peaks between the torsemide peaks on the suspension sample chromatogram were determined by separate vehicle RP-HPLC analysis to be due to OraPlus®[c]:OraSweet®[d] (chromatogram not shown).

Long-Term Strength and Stability Testing of Compounded Torsemide

Compounded torsemide strength averaged 96% for all samples at Day 0. Table 1 shows the strength results for room temperature (20–25°C) samples, and Table 2 shows the strength results for refrigerated (2–8°C) samples at subsequent time points.

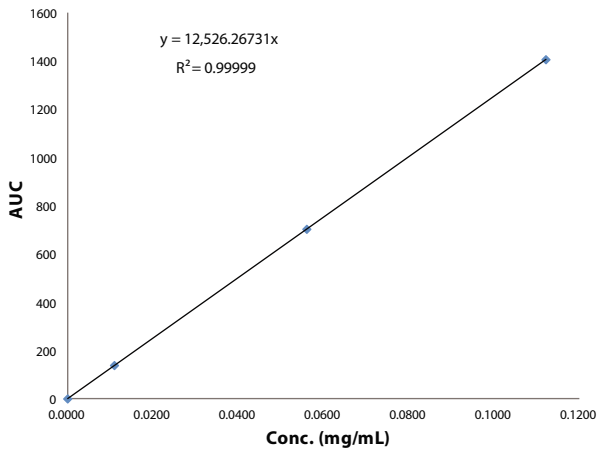

Fig 2. Reverse phase high-performance liquid chromatographic linearity standard curve for torsemide. AUC, area under the curve; Conc, concentration.

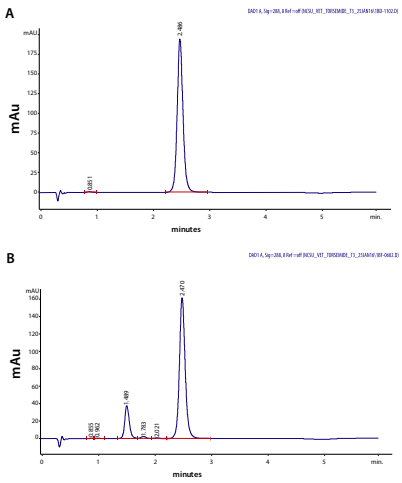

Fig 3. Sample reverse phase high-performance liquid chromatograms for: (**A**) Torsemide USP Reference Standard (Lot #: G0E293, 99.6% Pure); (**B**) Torsemide Oral Suspension Sample. mAu, milli absorbance units. The large peak at 2.47 min is torsemide (*). The small peak in A at 0.85 min is torsemide known impurity A (▼). The other smaller peaks between one and two minutes are from the vehicle OraPlus®[c]:OraSweet®[d] (#) (vehicle chromatogram not shown). The known impurities B, C, and E were not detected.

Table 1. Strength testing at room temperature (20–25°C).

Time point	% Strength Lot# 1	% Strength Lot# 2	% Strength Lot# 3	Mean ± SD % Strength	95% CI
Day 14	92	93	95	94 ± 2	90–97
Day 30	99	96	98	98 ± 2	94–102
Day 60	94	97	100	97 ± 3	90–104
Day 90	92	95	97	95 ± 2	89–100

SD, standard deviation; CI, confidence interval.

Table 2. Strength testing at cold refrigeration (2–8°C).

Time point	% Strength Lot# 1	% Strength Lot# 2	% Strength Lot# 3	Mean ± SD % Strength	95% CI
Day 14	91	94	94	93 ± 2	89–98
Day 30	92	94	96	94 ± 2	89–100
Day 60	95	91	96	94 ± 3	88–100
Day 90	89	92	96	92 ± 3	84–101

SD, standard deviation; CI, confidence interval.

The only individual strength that decreased below 90% was refrigerated Lot #1 at 90 days (89%) which is below the lower limit of acceptance for USP default stability for aqueous suspensions for oral use (90–110%), but when all 3 lots were averaged, the strength was acceptable (92 ± 3%)[b]. No samples stored at room temperature decreased below 90% strength during the 90-day period. The 95% CIs were acceptable for all time points for samples stored at room temperature but included strength results below 90% at all time points for samples stored at cold refrigeration.

Discussion

Our retrospective review of diuretic prescriptions at 2 veterinary referral centers demonstrated an increase in the use of torsemide in recent years. These results, however, may not be representative of torsemide use at other hospitals. The high number of compounded prescriptions from these institutions that were provided without previously published information regarding strength and stability supported the need for evaluation of compounded torsemide.

The results of our study support a BUD of 90 days for a suspension of torsemide intended for oral use in OraPlus®[c]:OraSweet®[d] buffered to an alkaline pH of 8.3. These initial investigations of compounded torsemide in 3 different unbuffered suspensions indicated a substantial loss of strength in 7 days. Because of the known alkaline pH of the injectable form of torsemide and a previous study that showed increased degradation in acidic conditions, we elected to alkalinize an aqueous-based suspension for further long-term analysis of stability.[9] The aqueous-based OraPlus®[c]:OraSweet®[d] solution was considered the most appropriate vehicle to further evaluate because it is not oil based, is suitably preserved for antimicrobial integrity, is widely available to compounders, is known to be palatable to dogs and cats, and is not associated with gastrointestinal upset. We did not reassess antimicrobial integrity at the higher pH, but the optimal pH for methylparaben (the preservative in OraPlus®[c]:OraSweet®[d]) is reported to be 4–8.[10]

Analyses of torsemide suspensions in OraPlus®[c]:OraSweet®[d] using RP-HPLC at each time point did not detect impurities other than torsemide-related compound A. All chromatograms showed only vehicle and torsemide components, including pure torsemide and this 1 known impurity. The results of long-term stability testing of this compounded torsemide 5 mg/mL suspension for oral use in OraPlus®[c]:OraSweet®[d], buffered to a final pH of 8.3 at room temperature (20–25°C) over 90 days, satisfied the strength requirements of 90–110% of label claim in USP <795> *Pharmaceutical Compounding—Non-sterile Preparations*[b]. Strength testing was slightly lower for refrigerated samples, but, only 1 refrigerated sample at 90 days was <90%, and the average of all 3 lots was >90%. Determination of BUD is currently based on average strength testing, and thus, these results satisfy USP requirements for a 90-day BUD[b].

We evaluated 95% CIs for strength and found they were <90% strength at all time points for refrigerated samples and just <90% strength only at 90 days for room temperature samples. The clinical importance of this finding is uncertain because 95% CIs currently are not utilized in BUD testing, but it indicates a potential stability advantage of room temperature storage over refrigeration. Variation in sampling technique or an effect of moisture or low temperature on the

physiochemical properties of torsemide could be causative, but these possibilities are speculative.

The stability data from our study support the assignment of a BUD of 90 days for torsemide 5 mg/mL suspension for oral use in 1:1 OraPlus®[c]:OraSweet®[d] buffered to a pH of 8.3, but a conservative BUD assignment of 60 days at room temperature may be justified. The results of our study are important, because adverse clinical effects have been associated with deterioration of compounded medication when using the default BUD provided by the compounding pharmacies.[7] The formula for the compounded torsemide suspension evaluated in our study will improve the ability to precisely dose this medication in small dogs and cats.

Footnotes

[a] Giatis IZ, Nguyenba TP, Oyama MA, et al. Use of Torsemide in 17 cats with advanced congestive heart failure (abstract). J Vet Intern Med 2014;28:1008A.

[b] United States Pharmacopeia, 795 Pharmaceutical Compounding —Non-sterile preparations, USP39–NF34 Page 617.

[c] OraPlus® Suspending Vehicle Ora-Sweet® flavoring, Perrigo Company, Allergan, MI, Lot#5302445.

[d] Ora-Sweet® flavoring, Perrigo Company, Allergan, MI, Lot#5262096.

[e] Torsemide, USP reference standard lot G0E293.

[f] Analytical Research Laboratories, 840 Research Parkway, Suite 546, Oklahoma City, OK 73104.

[g] Sodium Hydroxide 2N, Ricca Lot#2509F14 Exp:9/30/17 Arlington TX.

[h] Torsemide injection package insert. American Reagent, Inc., Shirley, NY 11967.

Acknowledgment

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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