Stability of Lisinopril in Two Liquid Dosage Forms

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BACKGROUND: Lisinopril is used in pediatric patients with hypertension. It is not commercially available as a liquid. Little is known about the stability of lisinopril in extemporaneously prepared liquid dosage forms.

OBJECTIVE: To determine the stability of lisinopril in 2 oral suspensions stored at 4 and 25 °C in plastic prescription bottles.

METHODS: Five bottles contained methylcellulose 1%:simple syrup NF (1:13) and the other 5 bottles had Ora Plus–Ora Sweet (1:1) at a lisinopril concentration of 1 mg/mL. Three samples were collected from each bottle at 0, 7, 14, 28, 42, 56, 70, and 91 days and analyzed by stability-indicating HPLC analytical method (n = 15).

RESULTS: At 4 °C, the mean ± SD concentration of lisinopril remained >95.1 ± 1.8% of the initial concentration in the methylcellulose formulation and 95.1 ± 3.2% of the initial concentration in the Ora Plus–Ora Sweet formulation throughout the 91-day study period. At 25 °C, the mean concentration of lisinopril remained >92.4 ± 2.2% of the initial concentration in the methylcellulose formulation for 8 weeks and 95.8 ± 2.3% of the initial concentration in the Ora Plus–Ora Sweet formulation throughout the 91-day study period. No changes in physical appearance in any samples were seen during this period.

CONCLUSIONS: Lisinopril can be prepared in either of 2 liquid dosage forms and stored for at least 13 weeks under refrigeration and 8 weeks at room temperature.

KEY WORDS: lisinopril, pediatrics, stability.

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Lisinopril may be used for the treatment of hypertension or congestive heart failure in pediatric patients. It is available in tablet formulations of 2.5, 5, 10, 20, 30, and 40 mg from at least 1 of 2 manufacturers (Prinivil by Merck[1] or Zestril by AstraZeneca[2]). No liquid dosage form of lisinopril is commercially available at this time.[3]

Infants and young children are unable to swallow tablets and also require dosage based on their body weight. For this purpose, an extemporaneously prepared liquid dosage form is needed with documented stability of the drug in easily accessible vehicles.

The stability of lisinopril in a liquid dosage form has been studied in syrup stored at 5 and 23 °C for 30 days[4] and at 25 °C over a 6-week period in a vehicle containing syrup (Ora Sweet SF) and an oral solution containing sodium citrate and citric acid (Bicitra).[5] It should be noted, however, that (1) many pharmacies preparing extemporaneous liquid dosage forms may not carry Bicitra, (2) the most common ready-to-use vehicle is a 50:50 mixture of a suspending agent and syrup (Ora Plus with Ora Sweet), (3) the liquid formulations are often stored under refrigeration (4 °C) for an extended period, and (4) long-term stability data would be useful for chronic therapy.

We designed a study to determine the stability of lisinopril in 2 liquid dosage forms (1 with ready-to-use vehicles, another prepared from common ingredients) stored at 2 temperatures (4 and 25 °C) in plastic prescription bottles over a 3-month period.

Methods

Lisinopril 10-mg tablets[a] were used to prepare the suspensions (Tables 1-3). The tablets were ground to a fine powder using a mortar and pestle, and 2 suspensions were then prepared: 1:13 methylcellulose 1%[6,b]

[a] Lot K9509, Merck & Co., West Point, PA

with simple syrup NF[c] added while mixing and 1:1 Ora Sweet[d] and Ora Plus[e] added while mixing. The concentration of lisinopril in each suspension was 1 mg/mL. Both lisinopril suspensions were stored in 10 amber plastic[f] prescription bottles (60 mL each). Five plastic bottles of each suspension were stored at 4 °C in a refrigerator,[g] and 5 other bottles were stored at 25 °C in a temperature-controlled water bath.[h]

The samples were taken after the bottles were shaken on a wrist-action shaker for 10 minutes and then allowed to stand for 2 minutes. The bottles were then gently inverted 3 times and the cap was removed; the samples were withdrawn from the center of the bottles at the midlevel of liquid. Three 500-µL samples were collected from each bottle on days 0, 7, 14, 28, 42, 56, 70, and 91 and analyzed in duplicate by an HPLC method modified in our laboratory (n = 15).[7] The HPLC method was proven to be stability indicating to ensure that the degradation products did not interfere with the measurement of lisinopril in suspensions. The pH was measured using a digital pH meter on each study day.

The appearance and color of the samples were assessed by observing them against black and white backgrounds, and any changes in odor were noted at each sampling time. The HPLC instrumentation included an HP 1050 pump,[i] HP 1050 auto sampler,[j] HP 1050 variable wavelength detector,[k] and an HP 3396A integrator.[l] Other equipment included a Zorbax C18 3.0 × 150 mm,[m] a digital pH meter,[n] Burrell Wrist Action Shaker,[o] and a Voretex Genie 2.[p] The chemicals and reagents were American Chemical Society or analytical grade and included acetonitrile,[q] methanol,[r] buffer solution pH 7,[s] buffer solution pH 4,[t] and buffer solution pH 10.[u] The mobile phase consisted of 43% water with 0.8% diethylamine[v] and 57% acetonitrile filtered through 0.45-µm nylon 66 filter,[w] then degassed with helium.

Stock solution of lisinopril[x] was prepared in methanol and diluted to yield concentrations of 1.5, 1.0, 0.5, 0.25, and 0.1 mg/mL. One hundred microliters of these solutions were then mixed with 1 mL of mobile phase and centrifuged; the supernatant was analyzed the same way as the samples. The flow rate was 0.4 mL/min. The detector was set at 220 nm and the injection column was 10 µL. The column was maintained at a temperature of 25 °C.

To establish the stability-indicating nature of the method, lisinopril 1.0 mg/mL, the vehicles alone, and their mixtures were subjected to forced degradation. This was done by acid (2.0M HCl)[y] and base (2.0M NaOH)[z] hydrolysis, oxidation (H_2O_2 0.3%),[aa] and heat at 80 °C. The samples were analyzed as described earlier every 30 minutes until approximately one-half of the lisinopril peak disappeared to show that the quantification of lisinopril was not influenced by degradation products. Each chromatographic run required about 10 minutes, and lisinopril eluted at about 3.8 minutes. The linearity was determined by linear regression analysis of lisinopril concentration versus peak areas of lisinopril standards. The correlation coefficient was >0.999, with a coefficient of variation <2.7% intraday and 3.3% interday. Lisinopril was considered stable at >90% of initial concentration.

Table 1. Preparation of Methylcellulose 1%[6]

Ingredient	Strength	Quantity
Methylcellulose powder	4000 centipoises	10 g
Methylparaben	200 mg	
Propylparaben	100 mg	
Purified water, USP		qs 1000 mL

Instructions: Heat 200 mL of purified water to boiling. Add the parabens and mix well. Wet the methylcellulose powder and add it to the hot parabens solution. Allow to stand for 15 minutes, remove from heat, and qs with cold purified water while mixing well with a magnetic stirrer. Keep mixing until a clear, homogeneous solution results.

Table 2. Preparation of Lisinopril Suspension in Methylcellulose 1% Syrup

Ingredient	Strength	Quantity
Lisinopril tablets	10 mg	10
Methylcellulose	1% with parabens	7.7 mL
Simple syrup, NF		qs 100 mL

Instructions: Crush the tablets and triturate to a fine powder in a mortar. Levigate the powder with methylcellulose gel into a uniform paste. Add simple syrup in geometric proportions with constant mixing and transfer to a graduate. Rinse the mortar with syrup, transfer to the graduate, and qs to 100 mL.

Results

The stability data for lisinopril in the 2 extemporaneously prepared suspensions stored in plastic bottles at 2 temperatures are presented in Table 4. In the suspension with simple syrup and methylcellulose 1%, the mean concentrations of lisinopril were >95.1% of the initial concentration at 4 °C over the 3-month study period and >92.4% of the original concentration at 25 °C for 8 weeks. In the suspension with Ora Plus–Ora Sweet, the mean concentration of lisinopril was >95.1% of the initial concentration at 4 °C and 95.8% of the original concentration at 25 °C during the 3-month period. No change in pH, appearance, color, or odor was noted with any of the samples during the course of this study.

Table 3. Preparation of Lisinopril Suspensions in Ora Plus–Ora Sweet

Ingredient	Strength	Quantity
Lisinopril tablets	10 mg	10
Ora-Plus		
Ora-Sweet		aa qs 100 mL

Instructions: Crush the tablets and triturate to a fine powder in a mortar. Levigate the powder with a small amount of the vehicle into a uniform paste. Add the vehicle in geometric proportions with constant mixing and transfer to a graduate. Rinse the mortar with vehicle, transfer to the graduate, and qs to 100 mL.

[c]Lot 88284E, Humco Laboratory, Texarkana, TX.
[d]Lot 7L6459, Paddock Laboratories, Minneapolis, MN.
[e]Lot 4E6462, Paddock Laboratories.
[f]Polyethylenephthalate bottles, OI Owens-Illinois, Toledo, OH.
[g]White-Westinghouse, White Consolidated, Columbus, OH.
[h]Lauda RM20, Brinkman Instruments, Westbury, NY.
[i]Hewlett-Packard, Analytical Products Group, Palo Alto, CA.
[j]Hewlett-Packard, Analytical Products Group.
[k]Hewlett-Packard, Analytical Products Group.
[l]Hewlett-Packard, Analytical Products Group.
[m]MAC-MOD Analytical, Chadds Ford, PA.
[n]Orion, model 701A, Orion Research, Boston, MA.
[o]Burrell, Pittsburgh, PA.
[q]Fisher lot 91090-24, Fisher Scientific.
[r]Fisher lot 910043-23, Fisher Scientific.
[s]Fisher lot 906524-24, Fisher Scientific.
[t]Lot 79F5609, Sigma Chemical, St. Louis, MO.
[u]Lot 8817KETG, Mallinckrodt, Paris, KY.
[v]Lot BS908, Burdick & Jackson, Division of Baxter, Muskegon, MI.
[w]Lot 0082205, Gelman Sciences, Ann Arbor, MI.
[x]Lot 49H4070, Sigma Chemical.
[y]Lot AB12KBSV, Mallinckrodt Specialty Chemical, Chesterfield, MO.
[z]Sodium hydroxide lot 0011ODX, Aldrich Chemical, Milwaukee, WI.

Discussion

Our data indicated that lisinopril was chemically and physically stable in 2 extemporaneously prepared suspensions for an extended period. The liquid preparation may improve the ease and accuracy of drug administration in infants and young children.

Documentation of stability in 2 formulations provides a choice for clinicians preparing an extemporaneous formulation. Those preferring a ready-to-use vehicle may choose Ora Plus and Ora Sweet, while those desiring to prepare a less expensive methylcellulose suspension may use its powder for compounding the suspension. Further, most countries may not have ready-to-use suspension vehicles (eg, Ora Plus, Ora Sweet) on their markets.

Our study extends the available lisinopril stability data on the 30 days of stability at 5 and 23 °C[4] and 6-week stability at 25 °C.[5] It offers a choice of 2 vehicles, as well as storage under refrigeration or at room temperature. The drug was stable for 8 weeks in one vehicle and 3 months in another.

Lisinopril is among many drugs not labeled for use in infants and children and yet is used routinely for their treatment. In such cases, the availability of extemporaneously prepared liquid dosage forms with documented stability becomes an important consideration in making decisions about whether to use these drugs. Our results make it possible for treatment using lisinopril in infants and young children.

Summary

An extemporaneous liquid formulation of lisinopril can be prepared in Ora Plus and Ora Sweet (1:1) and stored in plastic prescription bottles for 13 weeks under refrigeration or at room temperature without substantial loss of potency. It can also be prepared in methycellulose 1% and simple syrup NF (1:13) and stored in plastic prescription bottles for 8 weeks at room temperature and 13 weeks under refrigeration without significant loss of drug concentration.

Table 4. Stability of Lisinopril in Two Suspensions at 4 and 25 °C

	% Initial Concentration Remaining[a]			
	4 °C		25 °C	
Day	1% MC/Syrup[b]	OS/OP[c]	1% MC/Syrup[b]	OS/OP[c]
0	100% ± 0.97[d]	100% ± 1.98[e]	100% ± 1.28[f]	100% ± 2.03[g]
	pH 6.74 ± 0.02	pH 4.83 ± 0.03	pH 6.74 ± 0.03	pH 4.82 ± 0.02
7	100.21 ± 1.04	99.9 ± 1.84	100.27 ± 1.69	100.09 ± 1.99
14	99.63 ± 1.02	99.53 ± 1.72	98.21 ± 1.34	99.05 ± 2.13
28	99.17 ± 1.33	99.17 ± 2.12	97.15 ± 1.53	98.31 ± 2.31
42	98.47 ± 1.23	98.47 ± 2.03	94.62 ± 2.21	97.91 ± 2.41
56	97.22 ± 1.45	97.68 ± 2.37	92.37 ± 2.23	97.22 ± 2.53
70	96.93 ± 1.67	97.21 ± 2.98	90.76 ± 2.13[h]	96.45 ± 2.29
91	95.12 ± 1.83	95.12 ± 3.17	88.79 ± 2.83	95.79 ± 2.34

[a]Mean ± SD for 15 samples. None of the mean pH values changed during the study period.
[b]Methylcellulose 1% in syrup.
[c]1:1 mixture of Ora Sweet and Ora Plus.
[d]The actual concentration was 1.05 ± 0.01 mg/mL.
[e]The actual concentration was 1.00 ± 0.03 mg/mL.
[f]The actual concentration was 1.02 ± 0.02 mg/mL.
[g]The actual concentration was 1.03 ± 0.04 mg/mL.
[h]The concentration is <90% considering the SD.

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EXTRACTO

ANTECEDENTES: El lisinopril es usado en pacientes pediátricos con hipertensión, aunque no está disponible comercialmente en forma líquida. Se conoce muy poco sobre la estabilidad del lisinopril en las formas de dosificación líquidas preparadas improvisadamente.

OBJETIVO: El propósito del estudio fue determinar la estabilidad del lisinopril en 2 suspensiones orales almacenadas a temperaturas de 4 y 25 °C en botellas de prescripción plásticas por un período de 3 meses.

MÉTODOS: Tabletas de 10 mg de lisinopril cada una fueron utilizadas en la preparación de las suspensiones. Se prepararon 5 botellas conteniendo metilcelulosa 1%:jarabe simple FN (1:13) y otras 5 botellas conteniendo Ora Plus:Ora Sweet (1:1), a una concentración de lisinopril de 1 mg/mL. Cinco botellas de cada suspensión fueron almacenadas en un refrigerador a 4 °C, y otro grupo de 5 botellas de cada suspensión fue almacenado en un baño de agua a una temperatura controlada de 25 °C. Se coleccionaron 3 muestras de cada botella los días 0, 7, 14, 28, 42, 56, 70, y 91, y se analizaron a través del método analítico de la HPLC (por sus siglas en inglés) indicando estabilidad (n = 15).

RESULTADOS: A una temperatura de 4 °C, la concentración media del lisinopril se mantuvo sobre 95.1 ± 1.8% de la concentración inicial en la formulación de metilcelulosa y 95.1 ± 3.2% de la concentración inicial en la formulación de Ora Plus:Ora Sweet a través de los 91 días del estudio. A 25 °C, la concentración media del lisinopril se mantuvo sobre 92.4 ± 2.2% de la concentración inicial en

95.8 ± 2.3% de la concentración inicial en la formulación de Ora Plus:Ora Sweet a través de los 91 días del estudio. No se observaron cambios en apariencia física durante este período.

CONCLUSIONES: El lisinopril puede ser preparado en 1 de 2 formas de dosificación líquidas y puede ser almacenado por lo menos por 13 semanas bajo refrigeración y por 8 semanas a temperatura ambiente.

Brenda R Morand

RÉSUMÉ

INTRODUCTION: Le lisinopril est utilisé chez les enfants souffrant d'hypertension. Aucune formulation liquide n'est cependant disponible commercialement. De plus, on en connaît peu sur la stabilité des formulations extemporanées.

OBJECTIF: Cette étude avait pour but de déterminer la stabilité de 2 suspensions de lisinopril destinées à l'administration par voie orale.

MÉTHODES: Deux suspensions de lisinopril à 1% ont été préparées en utilisant un support différent. Une était à base de methylcellulose à 1% et de sirop simple NF (1:13), alors que l'autre utilisait un support d'Ora Plus et d'Ora Sweet (1:1). Chacune des 2 suspensions a ensuite été transvasée dans 10 bouteilles de plastique ambré. La moitié des bouteilles a été conservée au réfrigérateur (4 °C), alors que l'autre moitié était conservée à la température ambiante (25 °C). La teneur en lisinopril a été analysée par chromatographie liquide haute performance (HPLC) à 0, 7, 14, 28, 42, 56, 70, et 91 jours. À chaque fois, 3 échantillons étaient prélevés de chaque bouteille (n = 15).

RÉSULTATS: La teneur moyenne de lisinopril est demeurée au-dessus de 95.1 ± 1.8% de la concentration initiale avec la formulation à base de methylcellulose et au-dessus de 95.1 ± 3.2% de la concentration initiale avec la formulation à base d'Ora Plus:Ora Sweet, lorsque celle-ci sont conservées à 4 °C pendant 91 jours. À 25 °C, les concentrations moyennes sont demeurées au-dessus de 92.4 ± 2.2% de la concentration initiale avec la formulation à base de methylcellulose pendant 8 semaines et au-dessus de 95.8 ± 2.3% de la concentration initiale avec la formulation à base d'Ora Plus:Ora Sweet pendant 91 jours. Aucun changement de l'apparence physique des 2 suspensions n'a été observé.

CONCLUSIONS: Les 2 formulations liquides testées s'avèrent stables pendant au moins 13 semaines lorsque conservées au réfrigérateur et pendant au moins 8 semaines lorsque conservées à la température ambiante.

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