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CLINICAL INVESTIGATION

Chemical Stability of Extemporaneously Prepared Lorazepam Suspension at Two Temperatures

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The objective of this study was to determine the chemical stability of extemporaneously prepared lorazepam suspension (1 mg/mL) stored at two temperatures (4°C and 22°C) for 3 months. Lorazepam tablets marketed by two manufacturers (Mylan Pharmaceuticals and Watson Laboratories) were used to extemporaneously formulate two independently prepared suspensions. Each suspension was prepared using sterile water, Ora-Plus® and Ora-Sweet® to achieve a final concentration of 1 mg/mL. The two brands of tablets required different volumes of vehicles to prepare a pharmaceutically optimal suspension. The suspensions were stored in amber glass bottles at 4°C and 22°C for 91 days. Samples were analyzed by high performance liquid chromatography at baseline and on days 2, 3, 7, 14, 21, 28, 42, 63, and 91. The suspensions were considered stable if the mean lorazepam concentration remained greater than 90% of the initial concentration.

The chemical stabilities of these two extemporaneously prepared lorazepam suspensions were comparable throughout the study. Both lorazepam suspensions were stable for 63 days when stored at 4°C or 22°C, and both were stable for 91 days when refrigerated at 4°C. When stored at room temperature, the suspension prepared from the Watson tablet retained 88.9 ± 1.4% of the initial concentration on day 91 and was therefore considered unstable, while the suspension prepared from the Mylan tablet was stable for the entire 91-day study.

KEYWORDS: benzodiazepines, drug stability, extemporaneous formulation, lorazepam, suspensions

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BACKGROUND AND SIGNIFICANCE

There are numerous medications that are commercially unavailable in a liquid dosage form, which makes it challenging to administer these agents to children and adults who cannot swallow tablets or capsules. Thus, it is common practice for pharmacists to extemporaneously compound liquid preparations using the commercially available solid dosage form. While the stability of many extemporaneously prepared suspensions is already known,[1] currently there are no data on the stability of lorazepam suspension. Lorazepam is often administered enterally to children in the pediatric intensive care unit (PICU) in order to provide sedation or to prevent abstinence syndrome.[2,3] Due to its poor solubility in water, lorazepam solution (Intensol, Roxane Laboratories, Columbus, OH) is commercially formulated in a mixture of propylene glycol and polyethylene glycol. Propylene glycol is widely used in the pharmaceutical industry as a solvent for various oral and injectable preparations. When consumed in small quantities, propylene glycol is generally considered to be safe.[4] However, when lorazepam is administered in high doses, as is often necessary with long-term deep sedation in the PICU, the large amount of propylene glycol may cause

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adverse effects such as hyperosmolality, seizures, lactic acidosis, and cardiac toxicity in both adult and pediatric patients.[5-8] Furthermore, since both propylene glycol and polyethylene glycol are osmotically active, diarrhea may occur as a result of enteral administration of the liquid formulation of benzodiazepines.[2]

Complications associated with high doses of propylene glycol and polyethylene glycol may be avoided by administering an extemporaneously prepared lorazepam suspension from lorazepam tablets. Currently, lorazepam tablets are manufactured by a number of generic companies and these tablets vary in the type and quantity of pharmaceutical excipients. When tablets are used to formulate a liquid preparation, the type and quantity of excipients may affect the volume of water that must be added to disperse the tablets, and ultimately how much suspending agent is necessary to formulate the suspension. Therefore, the formulation and perhaps the suspension stability may vary when tablets from different manufacturers are used. The objective of this study was to determine the chemical stability of lorazepam suspension extemporaneously prepared using lorazepam tablets from two different manufacturers and to evaluate whether differences in the formulation have an effect on suspension stability.

METHODS

Preparation of Lorazepam Suspensions

Lorazepam suspensions were extemporaneously prepared to a final concentration of 1 mg/mL using 2 mg lorazepam tablets. Higher concentrations (e.g., 2 mg/mL) were not prepared due to the thickness of the final suspension. The first suspension was prepared using lorazepam tablets obtained from Mylan Pharmaceuticals, Inc. (Morgantown, WV; Lot# 1JO646), and the second suspension was prepared using lorazepam tablets obtained from Watson Laboratories, Inc. (Corona, California; Lot # 24202D99). The suspending and sweetening agents were Ora-Plus (Paddock Laboratories, Minneapolis, MN; Lot# 471719) and Ora-Sweet (Paddock Laboratories, Minneapolis, MN; Lot# 223185), respectively. Ora-Plus is a suspending vehicle whose ingredients include purified water, microcrystalline cellulose, carboxymethylcellulose, xanthan gum, and carrageenan. Ora-Sweet is a syrup vehicle that contains purified water, sucrose, glycerin, sorbitol, and flavoring. Each suspension was prepared by placing 180 tablets in a 12-oz amber glass bottle and adding the minimum volume of sterile water (Baxter, Deerfield, IL; Lot# G965053) necessary for tablet dispersion. The bottle was shaken until the tablets were dispersed and a slurry was formed. This method of preparation was selected in favor of using a mortar and pestle to crush the tablets since the latter resulted in significant drug loss during transfer to the final bottle. Ora-Plus was added by geometric dilution, followed by an adequate volume of Ora-Sweet to yield 360 mL of a 1 mg/mL suspension. The bottle was calibrated in advance to the final volume (360 mL) by measuring the total volume in a graduated cylinder and marking the bottle with a fill line. The actual volume of the three liquids required to formulate each suspension was as follows: for the Mylan product, 144 mL sterile water, 108 mL Ora-Plus and 83 mL Ora-Sweet; and for the Watson product, 48 mL sterile water, 156 mL Ora-Plus, and 146 mL Ora-Sweet. Each suspension was divided into ten 1-ounce amber glass bottles. Five bottles were stored under refrigeration at 4°C (range: 3–5°C), and five bottles were stored at 22°C (range: 21.5–22.5°C) using a temperature-controlled water bath.

Stability Testing

Chemical stability was determined by high performance liquid chromatography (HPLC) using a stability-indicating HPLC assay that was modified slightly for the analysis of a suspension.[9] The instrumentation consisted of a Hitachi HPLC system (Hitachi Ltd. Tokyo, Japan), which included an AS-2000 Autosampler, L-6200A Intelligent Pump, L-4200H UV/VIS Detector, and D-6000 Chromatography Data Station Software. Samples were injected onto a mBondapak C_{18}, 10 μm column (3.9 × 300 mm) (Waters, Franklin, MA). The mobile phase consisted of a 57:43 mixture of acetonitrile and water, and the flow rate was set at 1.6 mL/min. The UV detector monitored absorbance at 230 nm. Retention time for lorazepam and the internal standard were 3.0 and 4.6 minutes, respectively. To assess the stability-indicating nature of the method, lorazepam was forcibly degraded by heating to 90°C for three hours. This resulted in a 50 – 71% reduction in the lorazepam peak area, and a new non-interfering peak eluted at 4.3 minutes.

Concentration analysis was performed at

Table 1. Stability of extemporaneously prepared lorazepam suspensions at 4°C and 22°C. Results are reported as the mean (SD) for 5 replicates an=alyzed in duplicate (n=10). Initial concentration (Conc) is reported in mg/mL

		Percent of Initial Concentration							
	Initial Conc	Day 2	Day 7	Day 14	Day 21	Day 28	Day 42	Day 63	Day 91
Mylan (4°C)	0.98 (0.01)	99.8 (2.9)	100.8 (2.3)	100.1 (0.8)	99.2 (1.6)	101.3 (2.3)	99.8 (1.7)	97.0 (3.4)	96.8 (1.6)
Mylan (22°C)	0.98 (0.02)	100.7 (1.9)	101.7 (4.2)	101.0 (5.0)	98.1 (3.3)	99.3 (3.0)	98.0 (2.0)	94.0 (2.7)	94.2 (2.2)
Watson (4°C)	1.04 (0.01)	101.3 (0.9)	102.5 (1.2)	102.6 (2.8)	100.3 (0.4)	102.3 (1.5)	100.2 (1.5)	102.1 (2.1)	99.4 (2.7)
Watson (22°C)	1.03 (0.01)	102.2 (4.1)	101.6 (1.2)	99.6 (1.2)	96.8 (1.0)	98.3 (1.7)	93.8 (1.2)	90.9 (1.1)	88.9 (1.4)

baseline and on days 2, 3, 7, 14, 21, 28, 42, 63, and 91. On each day, samples were taken from each bottle for visual inspection of color changes and were immediately prepared for analysis. Each bottle was shaken vigorously for one minute, and a 1-mL aliquot was withdrawn and vortexed for 30 seconds. Two 100-µL samples were placed in separate microcentrifuge tubes and an equal volume of the internal standard solution (diazepam 0.5 mg/mL in methanol; diazepam lot# 105F0451; Sigma, St. Louis, MO) was added to each tube. The mixture was vortexed for 30 seconds and centrifuged at 10,000 rpm for 6 minutes. The supernatant from each tube was transferred into a glass vial and diluted with 1 mL of 60% methanol. The mixture was vortexed and a 25-µL sample was injected onto the column.

On each sample day, six calibration standards of lorazepam (Lot# 35F0115; Sigma, St. Louis, MO) were prepared in 100% methanol at concentrations ranging from 0.05 to 1.5 mg/mL. Peak-area ratios of lorazepam to the internal standard were plotted against the known concentrations of lorazepam and were analyzed by linear regression. Quality assurance samples were prepared on each test day using the commercially available lorazepam Intensol solution (Roxane, Columbus, OH) diluted with 100% methanol to a final concentration of 1.0 mg/mL. The mean correlation coefficient for the calibration curves was 0.9993 and the intraday and interday coefficient of variation for the quality assurance samples was < 1.6 % (n = 11). The mean accuracy of the quality assurance samples was 99.6% (n = 11), ranging from 96.5% to 101.8% of theoretical.

Data Analysis

Lorazepam concentrations are reported as mean ± standard deviation (SD). According to the USP, compounded substances shall not contain less than 90% of the theoretically calculated and labeled quantity of active ingredient.[10] Lorazepam suspension was considered stable if the mean concentration remained above 90% of the initial concentration.

RESULTS

The initial lorazepam concentrations and stability results are reported in Table 1. The mean concentration of the lorazepam suspension prepared with Mylan tablets was greater than 94% of the initial concentration for 91 days when stored at either 4°C or 22°C. Lorazepam suspension prepared with Watson tablets was stable throughout the 91-day study period when stored at 4°C; however, when stored at room temperature (22°C), the mean lorazepam concentration on day 91 was 88.9% of the initial concentration.

DISCUSSION

The results of this study demonstrate that an extemporaneously prepared lorazepam suspension is stable for 2 months when stored at 4°C or 22°C and stable for 3 months when refrigerated at 4°C. An interesting finding of this study was the slight difference in stability at room temperature when different brands of lorazepam tablets were used in preparing the suspension. Several explanations may exist for these findings, including the fact that different vehicle volumes were used in preparing each of the two suspensions. Different volumes were necessary due to the differences in tablet formulation and weight. The objective in preparing the suspension was to add the minimum volume of sterile water necessary for tablet dispersion. The Mylan product required

almost three times the volume of sterile water as compared to the Watson product in order to disperse the tablets. Between the two brands, this resulted in different ratios of water: Ora-Plus: Ora-Sweet.

It is well documented that, in general, more stable drug suspensions occur when the solubility of the drug is decreased by virtue of the solvent composition.[11] Conversely, as more drug moves into the aqueous phase, it becomes more susceptible to degradation. Moreover, the polarity of the solvent system also affects how drug moves into the aqueous phase and therefore may affect the stability.[11] Thus, it may be that the intrinsic physicochemical properties of lorazepam interacted with the different vehicle in a way that resulted in different stabilities. Other factors that may have contributed to different suspension stabilities include formulation differences in the tablets (e.g., particle size, fillers, binders, lubricants, etc.), which may have affected the interaction of suspended lorazepam particles with the liquid vehicles.

Regardless of the mechanism of instability, the results from this study raise a general concern about using a brand of tablet or suspension formulation that differs from that in a published report. Since data on the stability of more than one suspension formulation are usually unavailable, pharmacists should be aware of the potential for variability in the stability of suspensions that are extemporaneously compounded using tablets from different manufacturers or using different vehicle volumes. Notwithstanding the differences noted in the stability of the suspensions from the two different brand tablets, it should be underscored that extemporaneously prepared lorazepam suspension was stable for a minimum of 2 months when stored at room temperature and three months when stored under refrigeration. Clinically, this makes for a suspension that is stable for a sufficient period of time in order to make it useful for dispensing to patients.

It should be noted that the bottle preparation method as described using sterile water results in the dilution of the preservatives in both Ora-Plus and Ora-Sweet. Although data are lacking, this may theoretically increase the potential for bacterial and mold growth in the final product over a long period, especially when doses are being removed at frequent intervals without aseptic technique. This may be a compelling reason to choose refrigeration rather than room temperature for product storage.

CONCLUSIONS

Lorazepam suspension (1 mg/mL) extemporaneously prepared using Watson or Mylan lorazepam tablets demonstrated comparable stability during the 91-day study. Both suspensions were stable for 63 days at either room temperature or under refrigeration. At 91 days, both suspensions stored at 4°C retained ≥ 90% of the initial concentration. When stored at room temperature, the Mylan suspension was stable for 91 days while the Watson suspension was unstable.

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