JPPT

Clinical Investigation

Stability of Ziprasidone Mesylate in an Extemporaneously Compounded Oral Solution

Kelsey Green, PharmD[1] and Roy C. Parish, PharmD[2,3]

[1] Department of Pharmacy, LSU Health Sciences Center, [2]Department of Clinical Pharmacy Practice, College of Pharmacy, The University of Louisiana at Monroe, [3]Department of Medicine, School of Medicine, LSU Health Sciences Center, Shreveport, Louisiana

OBJECTIVES To formulate a liquid preparation of ziprasidone in a convenient concentration to allow dosing of less than 20 mg and of sufficient chemical and physical stability to enable an entire prescription or course of treatment to be prepared in a single batch.
METHODS Geodon for injection (ziprasidone mesylate), 20 mg/mL, was diluted to 2.5 mg/mL in a commercially available sugar-free and alcohol-free, flavored syrup and stored at room temperature under ambient fluorescent light illumination, at room temperature in darkness, and under refrigeration. The ziprasidone content was measured in samples at various time intervals using a stability-indicating high-performance liquid chromatographic method.
RESULTS When refrigerated, the ziprasidone syrup that was compounded in a commercially available, sugar-free and alcohol-free vehicle maintained at least 90% of stated potency for at least 6 weeks. Samples stored under other conditions were less stable, underscoring the manufacturer's labeling regarding refrigerated storage of the reconstituted injection.
CONCLUSIONS The findings suggest that chemical and physical stability are maintained for 2 weeks under refrigeration, allowing the convenience of compounding for the long-term needs of a particular patient, rather than daily compounding. The only storage condition we recommend is refrigeration at 5°C.

KEYWORDS extemporaneous compounding, high performance liquid chromatography, oral solution, stability, ziprasidone

J Pediatr Pharmacol Ther 2010;15:138–141

INTRODUCTION

Ziprasidone has emerged as a useful sedative in children. Doses of 5-20 mg per day have been shown to be safe and effective for tic disorder in children 7 to 16 years old.[1] In our search of the medical literature, we did not uncover clinical studies in younger children. Although Pfizer completed clinical trials of a 10-mg/mL suspension and the Food and Drug administration approved the formulation in 2006,[2] this product was never marketed.

The smallest dosage strength that is commercially available is a 20-mg capsule; hence, the prescribing of smaller doses poses problems in accurate measurement and delivery. In order to use this medication fully in the pediatric population, a convenient liquid formulation in a concentration that enables one to use a teaspoon or dropper for measurement is essential. The objective of our study was to formulate a liquid preparation of ziprasidone in a convenient concentration that is sufficiently stable to allow compounding of an entire prescription or course of treatment in a single batch.

ABBREVIATIONS HPLC, High Performance Liquid Chromatography; NIST, National Institute of Standards and Technology

Address correspondence to: Roy C. Parish, PharmD, ULM College of Pharmacy, Shreveport Campus, 1725 Claiborne Ave. Shreveport, LA 71103, email: rparis@lsuhsc.edu

MATERIALS AND METHODS

Currently, a liquid formulation of ziprasidone is prepared as a suspension using Geodon hydrochloride capsules (20-80 mg ziprasidone base each) or as a solution using Geodon mesylate injection (20 mg base/mL). Although it costs more, we elected to use the injection product, because we thought a solution is more pharmaceutically elegant and less susceptible to caregiver errors, such as incomplete shaking of a suspension. In addition, the low water solubility of the hydrochloride salt (0.3 mcg/mL)[4] would make stability assessment using high performance liquid chromatography (HPLC) impractical. In the injectable dosage form, ziprasidone mesylate is solubilized by complexation with a β-cyclodextrin.[4]

For a flavored vehicle, we chose Ora-Sweet (Paddock Laboratories, Minneapolis, MN). This commercially available compounding agent is a transparent, alcohol-free, flavored oral syrup with a pale pink color and a pleasant taste. Its listed ingredients are purified water, sucrose, glycerin, sorbitol, flavoring, citric acid, sodium phosphate, methylparaben, and potassium sorbate.[5]

Geodon injection and Ora-Sweet were obtained from pharmacy stock that was purchased from a local drug wholesaler, as were 60-mL, brown, plastic prescription bottles. HPLC-grade acetonitrile (Burdick & Jackson, Muskegon, MI) was purchased from VWR Scientific (West Chester, PA).

Vials containing ziprasidone mesylate, equivalent to 20 mg of ziprasidone base, were reconstituted with 1.2 mL of distilled water to yield a 20 mg/mL solution. This was further diluted *secundum artem* with Ora-Sweet to a final concentration of 2.5 mg/mL and divided into 60-mL lots, each of which was placed in a brown, plastic prescription bottle. One bottle was stored at room temperature (20°C-22°C) and ambient illumination at 700 Lumen, using daylight fluorescent 40-watt bulbs; another was kept at room temperature (20°C-22°C) but covered from light, and a third was stored in a conventional refrigerator (15°C). Temperatures were measured with a mercury NIST (National Institute of Standards and Technology)-traceable thermometer, and ambient lighting was measured with a light meter in incident mode. Both temperature and light conditions were maintained 24 hours per day.

Aliquots, 2 mL each, were taken from each bottle at 0, 4, 8, 12, 24 (1 day), 48 (2 days), 72 (3 days), 96 hours (4 days), 168 hours (7 days), 336 hours (14 days), 504 hours (21 days), and 1008 hours (42 days). Each sample was immediately frozen at 5°C in the pharmacy's freezer for parenteral medications and later transported without thawing to the College of Pharmacy laboratory, where they were stored at -80°C pending assay.

All samples were analyzed in duplicate over a 3-day period, using a modification of the stability-indicating assay developed and validated in our College of Pharmacy laboratory.[6] Briefly, samples were diluted 10-fold with distilled water and analyzed by HPLC using a Hitachi Elite LaChrom HPLC system (Hitachi High Technologies America, Pleasanton, CA) controlled by Hitachi EZChrom software (Agilent Technologies, Pleasanton, CA). Separations were made on an Agilent C18 column, 4.5×100 mm at 40°C with a mobile phase of 45% acetonitrile and 55% phosphate buffer of 0.01 M, pH 7.99, delivered at 2.0 mL/minute. Detection was by ultraviolet absorbance at 317 nm. These chromatographic conditions yielded a spectroscopically pure ziprasidone peak eluting at 5.46 minutes. The assay was calibrated over the range 0.5 to 4 mg/mL and was linear over this range with $r^2 = 0.999904$. The within-day and between-day coefficients of variation were 6% and 8%, respectively.

RESULTS

Formulation of ziprasidone mesylate for injection with Ora-Sweet as a flavored vehicle resulted in a pharmaceutically elegant formulation with an attractive appearance and pleasant taste. The concentration facilitates dose measurement with either calibrated droppers or oral syringes. After storage, all samples retained the pale pink color of the vehicle. The refrigerated and frozen samples were cloudy when cold, but cleared when warmed to room temperature for analysis. Samples stored at room temperature for more than 168 hours also clarified on warming, but had a pronounced yellow or brown color; these were not analyzed, as they had obviously undergone significant change.

The ziprasidone content of all samples is shown in Figures 1-3. The formulation stored at ambient temperature and light retained less than 90% of the original content after 48 hours.

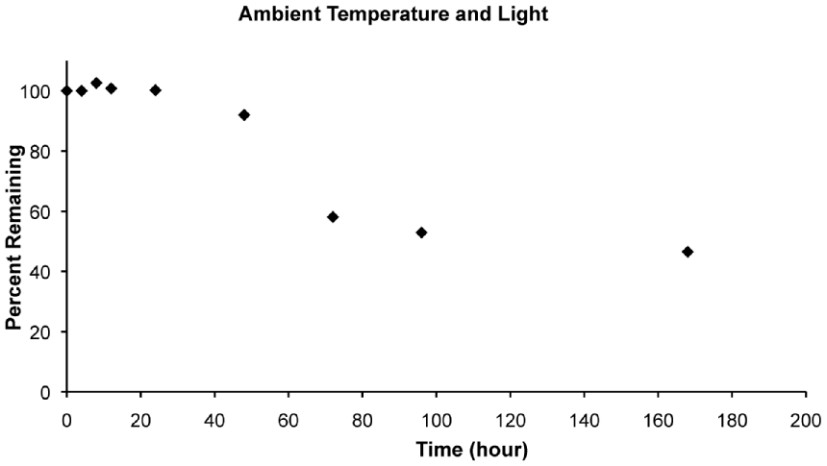

Figure 1. Formulation stored at 20-22°C and 700 Lumen daylight fluorescent lighting.

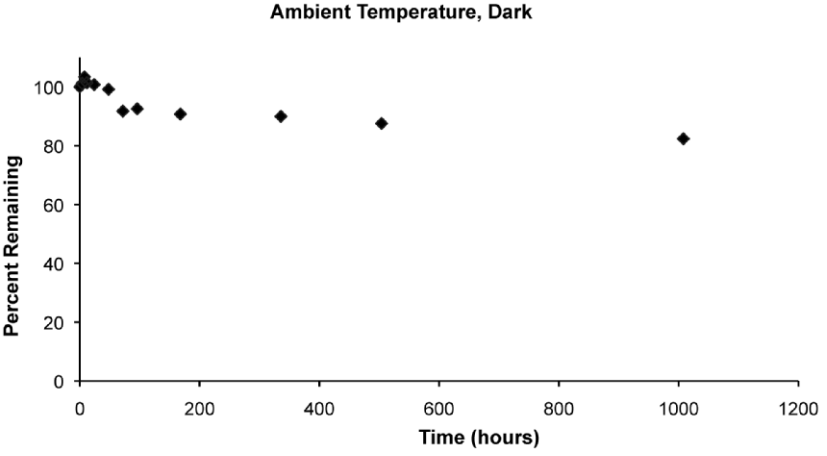

Figure 2. Formulation stored at 20-22°C and protected from light.

The formulation stored at room temperature, but protected from light, retained 90% or more of their original potency for up to 336 hours (14 days), with 87.6% potency at 504 hours (21 days) and 82.4% at 1008 hours (42 days). When stored under refrigeration, the formulation retained 90% of potency for the full duration of the study (6 weeks), with assay results 88.98% at 14 and 21 days and 90.98% at 6 weeks.

CONCLUSIONS

Formulation of ziprasidone for injection by simple dilution in Ora-Sweet syrup is a simple method of providing a pharmaceutically elegant formulation that can be easily compounded with a high degree of accuracy and precision. Although an oral suspension could be formulated at lower cost using oral capsules, use of the parenteral product eliminates weighing and inaccuracy due to incomplete recovery of powder from gelatin capsules. Moreover, the method avoids the deplorable but common practice of mixing powder from capsules in a simple vehicle and affixing a "shake well" label without thoughtful selection of suspending and thickening agents.

Storage of the product at room temperature in a lighted room is inappropriate, as more than10% loss of potency occurs within approximately 48 hours, even when stored in brown bottles. Of note, the Geodon information for the parenteral product contains a notice to protect the product from light.[7]

The preparation maintains satisfactory potency when stored at room temperature with protection against light for up to 60 days; the value of

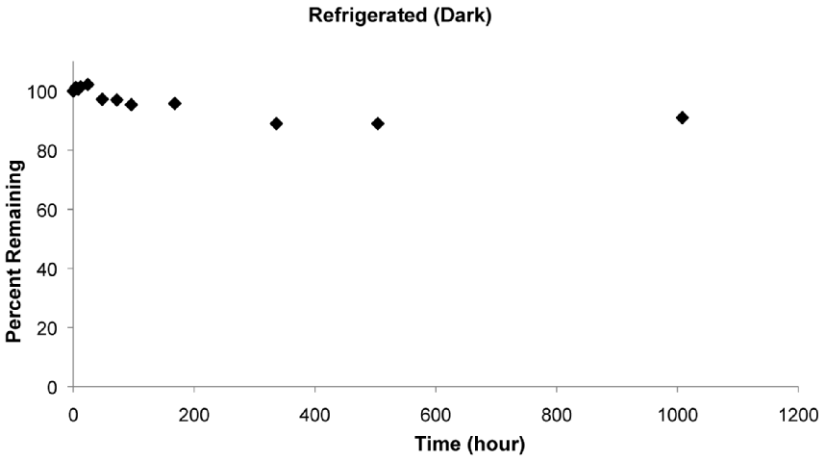

Figure 3. Formulation stored in refrigerator at 5°C.

88.98% at 14 and 21 days is within the error of the assay, and the value is clearly more than 90% at 6 weeks. However, we believe that the optimal storage condition is a temperature of 5°C or lower in a dark refrigerator, since potency that exceeds 90% was clearly retained throughout the 6-week period we studied. It should be understood, however, that these recommendations consider only potency issues; concerns about possible microbial growth may dictate shorter dating.

We have demonstrated an easy method of compounding a pharmaceutically elegant oral liquid formulation of ziprasidone in a concentration that facilitates accurate measurement of small doses and retains satisfactory potency for up to 6 weeks. This should allow compounding of an individual patient's ziprasidone solution in quantities sufficient for prolonged dosing, eliminating the need for daily compounding. It should be noted that this study addresses only chemical stability and not the issue of microbial contamination, which could be studied if standards of practice regarding storage need to be validated.

REFERENCES

1. Sallee FR, Miceli JJ, Tensfeldt T, et al. Single-dose pharmacokinetics and safety of ziprasidone in children and adolescents. J Acad Child Adolesc Psychiatry 2006;45:720-728.
2. Arenson DR, Qi, H, inventors; Pfizer, Inc., asignee. Ziprasidone Suspension. U.S. Patent 7,175,855. February 13, 2007.
3. FDA Approvals [database online] U.S. Food and Drug Administration website. Available at http://www.fda.gov/cder/rxotcdpl/pdpl_200603.htm. Accessed December 1, 2009.
4. Kim Y, Johnson KC, Shanker RM, inventors; Pfizer, Inc., asignee. Inclusion complexes of aryl-heterocyclic salts. U.S. Patent 6,232,304. May 15, 2001.
5. Personal communication, Dave Chinnick, R.Ph, Pharmacist, Paddock Laboratories, Inc., Minneapolis, MN, January 8, 2009.
6. El-Sherif ZA, El-Zeany B, El-Houssini OM, et al. Stability indicating reversed-phase high-performance liquid chromatographic and thin layer densitometric methods for the determination of ziprasidone in bulk powder and in pharmaceutical formulations. Biomed Chromatogr 2004;18:143-149.
7. Geodon [package insert]. New York, NY: Pfizer, Inc., 2007.