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CLINICAL INVESTIGATION

The Accuracy and Precision of Measuring Lorazepam From Three Liquid Preparations

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OBJECTIVES Commercially available lorazepam solution contains both polyethylene glycol (PEG) and propylene glycol. When large doses are administered for deep sedation in the pediatric intensive care unit (PICU), PEG may cause diarrhea, and the accumulation of propylene glycol may result in toxicity. These adverse effects may be avoided by preparing a slurry from crushed lorazepam tablets suspended in water immediately prior to administration. This slurry, which is extemporaneously prepared at bedside by nurses, lacks a suspending agent, and, therefore, the rapid settling of drug particles may produce suspensions that are not homogeneous. Thus, there may be significant inaccuracy and imprecision in dosage measurement. The objective of this study was to compare the accuracy and precision of lorazepam dosage measurement from three liquid preparations: 1) tablet slurry prepared at bedside by a nurse; 2) lorazepam suspension extemporaneously prepared by a pharmacist; and 3) the commercially available lorazepam solution.
METHODS Sixteen PICU nurses measured three doses of lorazepam (0.5 mg, 1.5 mg, 3.5 mg) in triplicate from each of the three liquid preparations using oral syringes. PICU nurses prepared the slurry by mixing crushed lorazepam tablet(s) with water and drawing up the appropriate dose in an oral syringe. Additionally, nurses drew up the appropriate dose from a pharmacist-prepared lorazepam suspension (1 mg/mL) and the commercially available lorazepam solution (2 mg/mL). All samples were analyzed by HPLC and the groups were compared using two-way ANOVA.
RESULTS Dosage accuracy for the slurry (91.2 ± 7.8%) and suspension (109.2 ± 4.9%) were significantly different from the commercially available solution (101.5 ± 3.1%) ($P < .05$). Imprecision in dosage measurement, as determined by the relative standard deviation, was greatest for the slurry (8.6%) as compared to the suspension (4.5%) and commercially available solution (3.0%).
CONCLUSIONS Dosage measurement from lorazepam slurry and suspension led to significant deviation from the intended dose. Dosage measurement using the slurry was the least precise among the three preparations.

KEYWORDS: administration, drug compounding, extemporaneous compounding, lorazepam, suspension, oral dosage forms

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INTRODUCTION

Limited availability of liquid drug formulations often poses a challenge in administering medications to children. Since most drugs are only available in a solid dosage form, accurate dosage measurement in young children is often difficult.[1] In some instances, a commercially

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ABBREVIATIONS: ANOVA, Analysis of Variance; HPLC, High Performance Liquid Chromatography; PEG, Polyethylene glycol; PICU, Pediatric Intensive Care Unit; RSD, Relative Standard Deviation

available liquid preparation may be undesirable due to adverse effects caused by inactive ingredients or pharmaceutical solvents, which are normally considered safe when consumed in small quantities. For example, sorbitol has been associated with gastrointestinal side effects in pediatric and adult patients, including diarrhea and bloody stools.[2-4] Similarly, the systemic accumulation of propylene glycol has been associated with hyperosmolality, seizures, lactic acidosis, and cardiac toxicity.[5-8] Therefore, extemporaneously prepared suspensions are sometimes preferred over commercially available liquid formulations in order to prevent excipient- or solvent-associated adverse effects.

An example of such a problem is the administration of large doses of commercially available lorazepam oral solution to mechanically ventilated children in the pediatric intensive care unit (PICU). Lorazepam Intensol Solution (Roxane Laboratories, Inc., Columbus, OH) contains both polyethylene glycol (PEG) and propylene glycol. When administered in large doses, as is often required for long-term deep sedation, PEG may cause diarrhea and the propylene glycol may result in the aforementioned toxicities.[9] One may avoid this problem by administering either lorazepam tablets or a lorazepam suspension; however, lack of data on the stability of lorazepam suspension has posed a problem. Thus, it has been common practice for PICU nurses in our institution to extemporaneously prepare a liquid preparation at bedside using the solid dosage form. Accordingly, nurses prepare a "slurry" by crushing tablet(s) and mixing with a known volume of water in a medication cup. An aliquot containing the desired dose is then drawn up into an oral syringe and administered to the patient, usually via nasojejunal feeding tube. The major problem with this extemporaneously prepared slurry is the potential for inaccurate dosage measurements, which may be due to the rapid settling of drug when no suspending agent is used. Moreover, this method is time consuming, requires careful calculation and preparation, and is not convenient or simple for parents to perform at home. Thus, parental preparation may increase the potential for medication errors. This problem is not unique to lorazepam and may apply to any drug that is insoluble in water for which stability data on extemporaneously prepared suspensions are lacking. For example, we have used this technique of preparing a bedside slurry for administration of other drugs, including nicardipine, amiodarone, amlodipine, and lisinopril.

A potentially superior method of dosage measurement is to administer a suspension that is extemporaneously compounded by a pharmacist using the appropriate suspending agents. Suspending agents function to keep insoluble drug homogeneously dispersed in a medium for a prolonged period and allow settled particles to be easily redispersed with a minimum amount of shaking. Thus, dosage inaccuracy and imprecision may be reduced when a water-insoluble drug is formulated as a true suspension in which stability is documented.

In this study, we hypothesized that drug dosages drawn up and measured by a nurse from a slurry prepared at bedside were inaccurate and imprecise. Moreover, we hypothesized that dosage measurements from an extemporaneously prepared suspension were superior in terms of accuracy and precision as compared to the slurry. Using lorazepam as a model water-insoluble drug, we tested these hypotheses with the primary objective being to evaluate and compare the accuracy and precision of dosage measurement by PICU nurses from three preparations: 1) lorazepam slurry extemporaneously prepared at bedside by the PICU nurse; 2) a suspension extemporaneously compounded by a pharmacist; and 3) the commercially available solution, which served as the active control.

MATERIALS AND METHODS

The study was approved by the University of Utah Institutional Review Board. Sixteen PICU nurses consented to participate in this prospective study. Each participant was asked to withdraw three doses of lorazepam (0.5 mg, 1.5 mg, and 3.5 mg) into oral syringes from the following liquid preparations: 1) Lorazepam Intensol Oral Concentrate (2 mg/mL) (Roxane Laboratories, Inc., Columbus, OH), which served as the active control formulation; 2) lorazepam suspension (1 mg/mL) extemporaneously prepared by a pharmacist; and 3) lorazepam slurry prepared by nurses at bedside using lorazepam tablets. All doses were drawn

Table 1. Instructions given to PICU nurse for preparing lorazepam doses

	0.5 mg	1.5 mg	3.5 mg
Lorazepam Slurry Preparation	1 mg tablet/5 mL of water	2 mg tablet/5 mL of water	2 × 2-mg tablets/5 mL of water
Volume to withdraw	2.5 mL	3.75 mL	4.38 mL
Lorazepam Suspension (1 mg/mL)			
Volume to withdraw	0.5 mL	1.5 mL	3.5 mL
Lorazepam Intensol Solution (2 mg/mL)			
Volume to withdraw	0.25 mL	0.75 mL	1.75 mL

up in triplicate. Nurses were queried on the technique used to prepare the slurry.

Preparation of Lorazepam Slurry by Bedside Nurses

Each nurse participant was dispensed the appropriate number of 2-mg lorazepam tablet(s) (Lot #1J1733; Mylan Pharmaceuticals, Inc. Morgantown, WV) to prepare a 0.5 mg, 1.5 mg, and 3.5 mg slurry in triplicate. Each dose was dispensed in a bag labeled with instructions that specified the volume of water in which to suspend the tablets along with the volume of the final aliquot in order to arrive at the appropriate dose (see Table 1). Aside from these instructions, no additional directions were provided on how to mix and prepare the doses. To simulate clinical reality, nurses were asked to measure the dose as they routinely do in their clinical practice and to draw up the medication during the day as time permitted. In order to minimize bias caused by greater attention to the quality and homogeneity of the slurry, all participants were informed only of the broad objectives of the study. No specific details were given regarding how the data would be evaluated and compared, and nurses were not made aware of the potential inaccuracies of mixing drugs in water. The oral syringes containing the study medication were immediately collected, labeled, and frozen at –70°C until analysis.

Extemporaneous Preparation of Lorazepam Suspension by a Pharmacist

Lorazepam suspension was extemporaneously prepared by a pharmacist/investigator (WR) on the morning of the study. One hundred and eighty 2-mg lorazepam tablets (Lot #1J1733; Mylan Pharmaceuticals, Morgantown, WV) were placed in a 12-ounce amber glass bottle and sterile water was added to disperse the tablets. The bottle was vigorously shaken for at least one minute until a slurry was formed. Thereafter, a suspending vehicle, Ora Plus (Lot #471719; Paddock Laboratories, Minneapolis, MN), and a sweetening agent, Ora Sweet (Lot #223185; Paddock Laboratories, Minneapolis, MN), were added by geometric dilution to achieve a final suspension volume of 360 mL. The ratio of sterile water to Ora Plus to Ora Sweet was approximately 40:30:30 to achieve the final concentration of 1 mg/mL. The suspension was shaken and immediately divided into sixteen 2-oz amber glass bottles. Lorazepam suspensions extemporaneously prepared in this fashion were found to be stable.[10]

Laboratory Analysis

Lorazepam concentration in each oral syringe was analyzed using a modified stability-indicating assay by high performance liquid chromatography (HPLC).[11] Briefly, the volume of medication contained in each syringe was recorded and the contents extracted with methanol. The internal standard diazepam (Lot #105F0451; Sigma, St. Louis, MO) was dissolved in 100% methanol and was added prior to HPLC analysis. Calibration standards were prepared by dissolving lorazepam (Lot # 35F0115; Sigma, St. Louis, MO) in 100% methanol to yield the following concentrations: 0.05, 0.025, 0.5, 0.75, 1.0, 1.5 mg/mL. Lorazepam concentrations versus the peak-area ratios of lorazepam to internal standard were analyzed by linear regression. The mean correlation coefficient was 0.9995 and the intraday and interday coefficients of variation for quality assurance samples were < 1.5% (n = 16). The accuracy of the assay ranged from 97.8% to 103.3% for a 1 mg/mL quality assurance sample (n = 16). The amount of lorazepam in each oral syringe was determined by multiply-

Table 2. Dosage measurements from three lorazepam liquid preparations made by 16 PICU nurses measured in triplicate (n = 48 samples per dosage level)

Lorazepam Dose	Intensol	Slurry	Suspension
0.5 mg			
Measured Dose (mg)	0.52 ± 0.02	0.45 ± 0.05	0.54 ± 0.03
Range of doses (mg)	0.48–0.56	0.32–0.51	0.47–0.62
Accuracy (%)	103.1 ± 3.2	89.1 ± 9.1*	108.4 ± 5.3*
Range of Accuracy (%)	97–112	64.2–102.5	94.1–124.8
RSD (%)	3.1	10.2	4.9
1.5 mg			
Measured Dose (mg)	1.52 ± 0.04	1.36 ± 0.11	1.64 ± 0.09
Range of doses (mg)	1.46–1.64	1.03–1.54	1.42–1.97
Accuracy (%)	101.5 ± 0.04	90.9 ± 7.6*	109.5 ± 5.7*
Range of Accuracy (%)	97–109.3	68.7–102.4	94.5–131.5
RSD (%)	2.4	8.3	5.2
3.5 mg			
Measured Dose (mg)	3.5 ± 0.1	3.27 ± 0.21	3.84 ± 0.12
Range of doses (mg)	3.31–3.85	2.78–3.83	3.45–4.07
Accuracy (%)	100 ± 2.7	93.4 ± 6.1*	109.6 ± 3.5*
Range of Accuracy (%)	94.6–110.1	79.6–109.5	98.5–116.3
RSD (%)	2.7	6.5	3.2

Data are reported as mean ± SD
RSD = Relative Standard Deviation, which represents the sample standard deviation expressed as the percentage of the mean.
**Within each dosage level, the difference in accuracy between Lorazepam Intensol (control) and the slurry/suspension dosage forms is greater than would be expected by chance (P < .05).*

ing the final concentration by the volume of the liquid preparation in the syringe.

Statistical Analysis

It was determined a priori that 16 nurses would be required to detect a 15% difference in accuracy among the three groups ($\alpha = 0.01$, $\beta = 0.2$). The measured dose was calculated for all nurse participants at each dosage level and the average was calculated for the three replicates. Accuracy was expressed as a percentage of the desired dose and precision was expressed as the relative standard deviation (RSD), which is the standard deviation expressed as a percentage of the mean. Descriptive statistics were used to report doses and accuracy. A comparison of accuracy was made between the three methods of preparation using two-way analysis of variance (ANOVA) with an all-pairwise comparison post hoc analysis. Statistical analysis was performed using SigmaStat (version 2.03, SPSS Inc., Chicago, IL).

RESULTS

Various techniques were used by nurse participants to prepare the lorazepam slurry, including 1) mortar and pestle to crush the tablets followed by the addition of water (5/16 nurses); 2) placing tablets in a 1-oz medication cup followed by the addition of water to cause tablet dispersion—followed by stirring (9/16 nurses); 3) placing tablets inside an oral syringe followed by the addition of water to cause tablet dispersion—followed by shaking (2/16 nurses). Two of the nurses used hot water to prepare the slurry. After preparing the slurry, some nurses withdrew the desired volume of slurry directly from the medication cup/mortar, while others withdrew the entire volume of slurry into the syringe and then discarded the unwanted volume.

The accuracy and precision of dosage measurement are reported in Table 2. Overall, the accuracy of dosage measurement from the lorazepam slurry and suspension was significantly different from the Intensol solution (control) for all doses combined (Table 3) and within each of the three dosage levels ($P < .05$). There was no statistical interaction between accuracy and the different doses used in the experimental design.

The imprecision in dosage measurement, as measured by the relative standard deviation,

Table 3. Overall accuracy and relative standard deviation (RSD) of dosage measurement for three lorazepam preparations for all doses combined

Preparation	Accuracy (%)	RSD (%)
Intensol Solution	101.5 ± 3.1	3.0
Slurry	91.2 ± 7.8*	8.6
Suspension	109.2 ± 4.9*	4.5

RSD = Relative Standard Deviation, which represents the sample standard deviation expressed as the percentage of the mean.
Data are reported as mean ± SD.
The difference in accuracy among the three dosage forms is greater than would be expected by chance after allowing for effects of differences in dose ($P < .001$).
**$P < .05$ as compared to Intensol solution (control)*

was almost three-fold higher in the slurry formulation than the Intensol solution and almost two times greater than lorazepam suspension (Table 3).

DISCUSSION

Since liquid formulations of pharmaceuticals are not always commercially available, it is often necessary for pharmacists to prepare suspensions extemporaneously. This is particularly common in children's hospitals where dozens of suspensions are routinely prepared.[12] Oftentimes, however, a pharmaceutical suspension may be unstable or stability data may be lacking, thus making it unsuitable for extemporaneous preparation by the pharmacist. These situations may be problematic for young or critically ill children who must be given a liquid dosage form. In such cases, nurses will often measure the appropriate dose at bedside by extemporaneously preparing a slurry in water. Aliquots of the slurry are measured in an oral syringe so as to arrive at the appropriate dose. If the drug is water-soluble and the solution is homogeneous, accurate dosage measurement using this technique does not pose a problem, as long as the drug is stable in water. However, if the drug is water-insoluble (e.g. lorazepam), the lack of a suspending agent in these slurries may cause the active drug to rapidly settle, thus increasing the potential for inaccurate dosage measurement.

Results from this study demonstrate the dosage inaccuracy and variability associated with extemporaneously preparing a slurry made from a solid dosage form. Although various techniques were used by PICU nurses to ensure that the slurry was well mixed and the proper lorazepam dosage was withdrawn, dosage measurement from the slurry preparation resulted in doses ranging from 64.2% to 109.5% of the intended dose. Accuracy of dosage measurement was particularly problematic at the lowest dose (0.5 mg) where just 89.1% (range 64.2–102.5%) of the desired dose was measured. Furthermore, as one might expect, the precision of dosage measurement was poor with the slurry preparation as the RSD ranged from 6.5% to 10.2%. Although there is no USP standard for extemporaneously compounded lorazepam suspensions, the USP standard for uniformity of dosage units in a commercially manufactured suspension may serve as a reasonable benchmark against which the accuracy and precision measurements in this study may be compared. According to these standards, no more than 1 unit of 30 tested may be outside the range of 85% to 115% of the label claim and no unit may be outside the range of 75% to 125%.[13] In addition, RSD may not exceed 7.8%. For the three doses tested in this study, accuracy fell outside of the acceptable range on all occasions and the RSD exceeded the USP standard for two of the three doses. It is noteworthy that the error and imprecision of dosage measurement from the slurry may theoretically be magnified when the slurry is prepared in an outpatient setting by caregivers who are not as skillful or familiar with preparing medications for administration. Although underdosing lorazepam by 5–10% in the PICU may not always be clinically significant, this preparative technique may pose a more serious risk when used with medications that have a narrow therapeutic index.

A secondary objective of the study was to determine if the accuracy and precision of dosage measurement from an extemporaneously prepared lorazepam suspension was superior to the slurry. Our group has found that lorazepam suspension (1 mg/mL) is stable for at least 2 months at room temperature.[10] This extemporaneous formulation may be useful when a patient does not tolerate the propylene glycol or PEG found in the commercially available solution. In this study, the suspension resulted in measured doses that exceeded the intended amount by 8.4% to 9.6%, although only once did it fall outside the USP standards for content

uniformity (i.e., for the 1.5 mg dose). Overall, the suspension resulted in less variability in dosage measurement than the slurry with all RSD (range 3.2% to 4.9%) falling within the USP standards. This was similar to the precision noted with the Lorazepam Intensol solution (RSD 2.4% to 3.1%), which served as the active control. The overestimation of the dose with the suspension was consistent among all nurses and was not a result of data outliers. This revealed an unexpected problem with the extemporaneously prepared suspension, i.e. the potential for inaccuracy in the concentration, which may be explained by the quasi-quantitative fashion in which extemporaneous suspensions are prepared. Thus, in the case of this study, the suspension concentration was likely to be somewhat greater than 1 mg/mL. This is consistent with the fact that almost every dose measured from the suspension (n = 144) was above 1 mg/mL, while the "gold standard" Intensol solution and quality assurance samples yielded no such systematic deviation. The results from this study indicate that the accuracy of dosage measurement may not be significantly improved with the use of pharmacist-compounded suspensions, however the precision of repeated dosage measurements is superior to that from the slurry preparation.

The limitations of this study include the possibility that nurses were more vigilant and careful in their preparation of the slurry and in measuring the doses. This suggests that there may be more variability in everyday practice than what was measured in this study. We attempted to minimize the potential for bias by not informing nurses of specific objectives and rationale for the study. Furthermore, we attempted to simulate reality by having nurses prepare the doses during the day and while caring for their patients.

In summary, extemporaneous preparation of liquid formulations is often imperative in order to facilitate administration of some medications to children, and this study should not dissuade the use of these compounded dosage forms when appropriate. However, clinicians should be aware of the potential for underdosing and significant variability in dosage measurement when slurries of water-insoluble drugs are prepared at bedside. Thus, other alternatives for medication administration should be sought whenever possible, particularly when dosage accuracy is critical. Moreover, pharmacists should be aware of the potential for dosage inaccuracy in extemporaneously prepared suspensions, which may be related to the method of preparation. Further study is needed to determine how often extemporaneously prepared suspensions deviate from the intended concentration, and to determine how much between-pharmacist variability exists in their preparation.

CONCLUSION

The accuracy and precision of dosage measurement using the slurry was poor, evidenced by significant underdosing and a relative standard deviation that was almost three-fold higher than the Intensol solution and almost two times greater than lorazepam suspension. Although the extemporaneously prepared suspension did not significantly improve the accuracy of dosage measurement, it may provide a more convenient and precise method of measuring doses of drugs for both the inpatient and outpatient setting.

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