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ORIGINAL RESEARCH

Liquid Medication Dosing Errors: Comparison of a Ready-to-Use Vigabatrin Solution to Reconstituted Solutions of Vigabatrin Powder for Oral Solution

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ABSTRACT

Introduction: Vigabatrin (VGB) is intended for use by caregivers of infants (1 month to 2 years old) diagnosed with infantile spasms (IS). Commercially available vigabatrin powders require caregiver reconstitution prior to oral administration. This study compared the ability of caregivers to accurately provide a targeted dose of vigabatrin using a ready-to-use (RTU) vigabatrin oral solution (VGB-RTU solution) and SABRIL® (vigabatrin) powder for oral solution, Lundbeck LLC, (vigabatrin powder) without instruction from a healthcare professional.

Methods: A crossover comparative usability study with 30 lay users (15 caregivers with vigabatrin powder experience and 15 oral-syringe/medication preparation naïve users) which required users to deliver a single dose of both VGB-RTU surrogate solution and vigabatrin powder to a sample collection bottle was performed. Doses were measured analytically with a primary endpoint to deliver doses within ± 10% of the target dose of 1125 mg.

Results: All 30 participants administered VGB-RTU solution doses within ± 5% of the target, while only 23/30 of the vigabatrin powder doses were within ± 10%. All naïve users delivered vigabatrin doses using VGB-RTU solution within ± 5% of the target; whereas only 13/15 delivered doses within ± 10% for vigabatrin powder. All experienced vigabatrin users delivered calculated vigabatrin doses using VGB-RTU solution within ± 3%; whereas only 10/15 delivered doses within ± 10% for vigabatrin powder. Users were equally able to accurately deliver the prescribed volumes of both products. Calculated doses of VGB-RTU solution (mg) were significantly less variable ($p < 0.0001$) and more accurate ($p < 0.01$) than doses of vigabatrin powder.

Conclusion: Caregivers delivered more accurate and less variable doses of the ready-to-use solution compared to solutions prepared from vigabatrin powders for oral solution. These differences were shown to be due to caregiver errors in reconstituting vigabatrin powders for oral solution.

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PLAIN LANGUAGE SUMMARY

Vigabatrin, an approved treatment for infants diagnosed with infantile spasms (IS), is available as a powder for oral solution and as a ready-to-use solution. Vigabatrin doses are frequently modified by physicians during treatment. Vigabatrin powders require caregivers to perform a multistep preparation process before measuring out the prepared solution; whereas a ready-to-use solution can be measured directly. A study with 30 lay users (15 caregivers with vigabatrin powder experience and 15 users without oral syringe experience) required users to deliver a single dose of both products to a sample collection bottle (representing a child's mouth) without instruction from a healthcare professional. This study's goal was to determine whether caregivers could provide accurate doses within ±10% of the target dose of 1125 mg using both the ready-to-use vigabatrin solution and a commercially marketed vigabatrin powder for oral solution. Delivered doses were measured, and all 30 participants administered calculated doses of the ready-to-use solution within ±5% of the target. Only 23 of 30 vigabatrin powder doses were within ±10%. Users were equally able to accurately deliver the prescribed volumes of both products proving that differences in accuracy and variability were due to caregiver errors that occurred when caregivers made a solution using the vigabatrin powder product. The study concluded that caregivers provided more accurate ($p<0.01$) and less variable ($p<0.0001$) doses (mg) of a ready-to-use vigabatrin oral solution compared to doses prepared and provided from commercially available vigabatrin powders.

Keywords: Dosing errors; Epilepsy; Infantile spasms; Oral solution; Powder; Reconstitution; Vigabatrin

Key Summary Points

Treating infants for infantile spasms with vigabatrin has historically required caregivers to accurately reconstitute solutions from powders twice daily.

This study examined the ability of caregivers to provide a target dose of 1125 mg vigabatrin using caregiver-reconstituted solutions prepared from a commercially available vigabatrin powder, and the same dose using a ready-to-use vigabatrin surrogate solution without instruction from a healthcare professional.

Caregivers delivered more accurate and precise doses of a ready-to-use solution compared to solutions prepared from vigabatrin powders.

Dosage errors were proven to be related to the reconstitution process rather than the final dose administration step.

This study determined that using a ready-to-use solution was significantly more likely to result in caregivers providing consistent and correct vigabatrin doses compared to vigabatrin powder.

INTRODUCTION

Infantile spasms (IS), sometimes referred to as West syndrome, was first described in a letter to the editor in *The Lancet* by William West, a British physician in 1841, which described the clinical features of a seizure disorder that manifested in his own son at age 4 months [1]. The International League Against Epilepsy adopted the term "infantile epileptic spasms syndrome" (IESS) to encompass infants presenting with epileptic spasms, with or without fulfilling all the criteria for West syndrome. IESS is associated with high rates of mortality and morbidity, lifelong refractory seizures, and extraordinary healthcare costs [2]. Children with IESS experience ongoing epileptic activity contributing to

severe cognitive and behavioral disabilities associated with a progressive cognitive decline [3].

Infantile spasms is a unique and rare disorder with an incidence of 2–3.5 per 10,000 live births; this is roughly 2000–2500 new cases in the USA annually [4]. The onset spans from the first week of life to 4 years, with an average onset age of 3–7 months [5]. The diagnostic challenge of IS is magnified by the urgency of treatment, as even a brief delay, as little as 1 week, has been associated with poor long-term neurodevelopmental outcomes [6]. Adrenocorticotropic hormone (ACTH), vigabatrin, and oral corticosteroids are major therapies used in the USA and Europe, with variable efficacy for children with IS [7].

The International Tuberous Sclerosis Complex (TSC) Consensus Group recommends VGB as first-line treatment, as it has been shown to be the most effective treatment in this population of patients with IS [8].

Vigabatrin was originally approved in the USA by the Food and Drug Administration (FDA) in 2009 in sachets containing 500 mg of vigabatrin powder that must be reconstituted by caregivers prior to oral dosing as monotherapy to treat IS in pediatric patients 1 month to 2 years of age [9]. In 2024, the US FDA also approved VIGAFYDE™ (Pyros Pharmaceuticals, Inc.), a ready-to-use 100 mg/mL vigabatrin oral solution [10]. This ready-to-use solution eliminates the reconstitution steps (and associated mixing time) required for vigabatrin powders for oral solution.

Both VGB products may be administered with or without food, and both contain 0.0 mg carbohydrates. Doses are based on the patient's weight and range from 50 to 150 mg/kg/day in two divided doses [9, 10].

For products administered to patients in the dosage form provided by the manufacturer, current Good Manufacturing Practice (cGMP) regulations ensure that a product is safe for use, and it has the strength claimed. Although vigabatrin powders are manufactured under cGMP conditions, unlike a ready-to-use oral solution, they are not administered to the patient in this dosage form. Twice daily, immediately prior to dosing, caregivers using powder formulations must follow a multistep procedure that, even for the same patient, may require the use of differing amounts of packets and water to prepare a solution with a final concentration of 50 mg/mL of vigabatrin. The potential for caregivers to make reconstitution errors is amplified since identifying a proper vigabatrin dose requires the healthcare professional to make dosage adjustments as they titrate the child's dose over time. As a result, the caregiver must prepare differing doses of vigabatrin as the dosage is titrated.

The objective of this study was to compare the ability of caregivers to accurately prepare a specific targeted dose of vigabatrin using a surrogate solution representing a ready-to-use vigabatrin oral solution (VGB-RTU solution) and an FDA-approved vigabatrin powder for oral solution (vigabatrin powder) without instruction from a healthcare professional. We hypothesized that a ready-to-use solution manufactured under cGMP standards could eliminate the potential for errors associated with the preparation of solutions by caregivers resulting in more accurate and precise doses being provided to infants.

METHODS

This study assessed the accuracy and variability of doses administered using a surrogate of VGB-RTU solution and vigabatrin powder. For the purposes of this study, the acceptable variability of target dosing was ± 10% of a target dose of 1125 mg (i.e., 1013–1238 mg). Additionally, the variability of dose delivered, along with variability and accuracy within subgroups (naïve and experienced users), was investigated.

A comparative, open label, crossover design was used during this study. Naïve participants ($n = 15$), representing caregivers of newly diagnosed infants, were either parents of young infants or adults of childbearing age who plan to have children who did not have prior experience using oral syringes (naïve) to provide medication. Per the protocol, experienced participants ($n = 15$) were caregivers who had administered vigabatrin in powder form to a child within the last 4 years; however, as a result of difficulties in enrolling caregivers of infants with IS, the study included two caregivers whose last experiences

exceeded this window. The study was conducted at facilities in Boston, MA, and Chicago, IL. This nonclinical study was approved by a national Institutional Review Board, Castle IRB (Chesterfield, MO). The investigation was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments, and was consistent with Good Clinical Practice and applicable regulatory requirements. Informed consent was obtained from participants prior to performing any study-related procedures.

The study excluded healthcare providers; those who had participated in market research studies within the past 6 months; had an occupation within market research, advertising, or a pharmaceutical/medical device company; or who were sharing a household with an individual working in those fields. Experienced participants averaged 40 years old (range 33–55 years old) while naïve participants averaged 28 years old (range 18–37 years old). Sixteen of 30 participants were male. The study was not powered sufficiently to detect differences between male and female caregivers.

The study was representative of a real-world situation that may be encountered by caregivers at home, and included a simulated kitchen environment equipped with all items required to successfully prepare the products per their labeling (i.e., measuring and preparation utensils, and liquids for reconstitution). A trained moderator, responsible for observing the participant's interactions with each product and documenting study observations, was in the room with the participant. The participant could sit or stand (participant's choice) at a counter or table to perform the simulated-use product preparation tasks.

VGB-RTU solution was provided in multidose 150-mL bottles with tamper-resistant foil seals and child-resistant caps. The VGB-RTU solution in this study, per FDA request, did not contain vigabatrin. This surrogate VGB-RTU solution, however, mirrored the physicochemical and viscosity characteristics of VIGAFYDE™. Since the concentration of vigabatrin in a ready-to-use solution is controlled by the approved manufacturing process and release testing rather than by the participant's ability to prepare a correctly concentrated solution, the theoretical dose of vigabatrin is proportional to the volume of solution delivered. Per the proposed labeling, a syringe adapter and reusable 6-mL syringe with 0.25-mL graduations were supplied to each participant. Commercial VIGAFYDE™ solution is sweetened with a non-caloric sweetener (sucralose) and contains a mild mint flavor.

SABRIL® powder for oral solution was provided in packets containing 500 mg vigabatrin, each of which must be diluted by the caregiver with 10 mL of water (to produce a vigabatrin concentration of 50 mg/mL) prior to drawing up the prescribed dose using the provided 3-mL or 10-mL oral syringes. SABRIL® powder contains no sweetener nor taste masking agents.

VGB-RTU solution and vigabatrin powder were evaluated through simulated use scenarios (including analytical analysis). This crossover study required participants to prepare both products. If participants had previously used vigabatrin powder, this scenario was performed first. The order in which naïve participants performed each scenario was conducted in accordance with the randomization schedule. Participants were provided with the FDA-approved labeling for SABRIL® powder for oral solution, and labeling similar to that approved for VIGAFYDE™, and asked to provide a single dose of 1125 mg. No verbal instructions were provided, and the observers were not allowed to answer any questions. A total of 2 h was allocated for the participants to complete the tasks required to prepare both products. Participants delivered doses into a sample collection bottle to simulate the mouth of an infant. Actual infants were not included in this study. Each total delivered dose was weighed by a trained analyst with a calibrated Mettler Toledo XS6002S top loading analytical balance (precision ± 0.05 g; CV < 0.10%), and the weights were recorded to the hundredths place. The volume of the delivered dose was calculated on the basis of the density of the solution (VGB-RTU solution = 0.9976 g/mL, reconstituted vigabatrin powder = 1.000 g/mL).

Since the concentration of vigabatrin in VIGAFYDE™ solution is controlled by the manufacturer, the theoretical dose of vigabatrin administered (mg) using the VGB-RTU solution was calculated using the theoretical concentration of vigabatrin (100 mg/mL) multiplied by

the volume of solution delivered. The dose of vigabatrin from solutions of vigabatrin powder in milligrams was calculated by multiplying the volume of solution delivered times the concentration of each prepared vigabatrin solution (in mg/mL) determined using a validated high-performance liquid chromatography (HPLC) assay. At least two control samples prepared by a trained analyst were interspersed in the randomization matrix each day, and were provided along with the study samples to the testing laboratory. The identities of the control samples were blinded to the laboratory personnel and were used to verify that the analyses performed by HPLC remained in a state of control throughout the study.

Study personnel collected sample weights, performed sample blinding, and shipped duplicate sample and control sample aliquots to the testing laboratory in real time after each day's session in Boston. Samples from Chicago were shipped to the blinding facility for processing (i.e., weights, blinding, and aliquot preparation) at the end of each day prior to shipping the blinded sample aliquots to the testing laboratory.

Findings were analyzed by experience level, sample weights, sample volumes, vigabatrin doses in milligrams, and vigabatrin concentrations in milligrams per milliliter.

Reconstituted solutions of vigabatrin powder were diluted and tested using a HPLC assay based on the USP assay method described in the *Vigabatrin for Oral Solution* monograph after verification of system suitability, linearity, accuracy, precision, range, standard stability, and sample stability. Daily HPLC sequences met system suitability. Linearity was demonstrated to be acceptable with a correlation coefficient of 0.999995. Accuracy demonstrated a mean recovery ($n=9$, 3 levels) of 100.0% and a percent relative standard deviation (RSD) of 0.3% (recovery 99.0–101.0%, ≤ 1.0% RSD). Precision was 0.1% RSD (≤ 1.0%). The method was shown to be accurate, linear, and precise, with a range of 1.0–3.0 mg/mL corresponding to 50–150% of the sample concentration after a 25-fold dilution. If samples fell outside of the validated range, dilutions were adjusted prior to reanalysis to ensure that all responses fell within the linear range. Sample stability was verified in sample bottles for 14 days and Eppendorf tubes for 4 days when stored at ambient conditions.

Data was evaluated for normal distribution. Consistently for all outcomes measures, VGB-RTU solution outcome measures were found to be normally distributed, while measures within the vigabatrin powder group did not satisfy normality evaluation via plots or Shapiro-Wilks testing. As such, a regression analysis using a generalized linear model with log transformation (log-link) of dose delivered, while accounting for repeated subject crossover design and controlling for subject experience in administering vigabatrin powder, was used to transform the data (SAS Proc Genmod). After transformation, log-transformed outcome measures satisfied normality assumptions. Transformed data were used to assess the variability of dose delivered and percentage dose delivered. Differences in proportions of dose deviation greater than 2% and 5% were reported as raw percentages with p values from two-sided Fisher's exact tests. Applied statistical tests were two-sided, with statistical significance set at $\alpha \leq 0.05$. Because the data for vigabatrin powder was skewed and highly variable, log transformation was required. As a result, the data set was determined to be insufficiently powered to detect differences in accuracy or variability between experienced and naive users.

RESULTS

The differences in the ability of naïve and experienced caregivers to provide a target dose of 1125 mg using VGB-RTU solution and vigabatrin powder are readily observable when the distribution of doses administered by each participant group are presented graphically (Fig. 1). Study results demonstrated that despite the small sample size, for all measures except dose volume, caregivers were significantly more likely to deliver more accurate and less variable calculated doses using VGB-RTU compared to reconstituted solutions of vigabatrin powder (Table 1).

The raw data revealed that the number of participants who administered a vigabatrin dose within ± 10% of a 1125-mg target dose

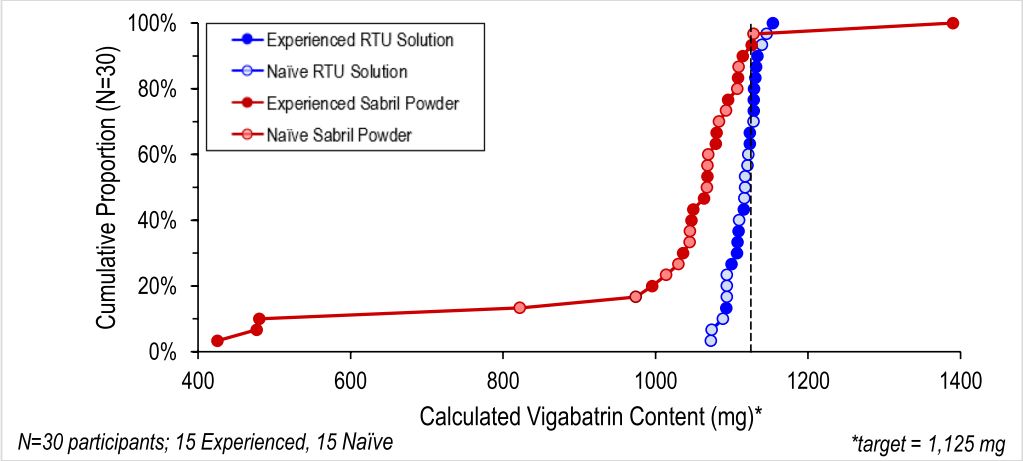

Fig. 1 Distribution of dose administered by participant group

Table 1 Statistical comparisons ($N = 30$ participants; 15 experienced, 15 naïve)

		VGB-RTU Solution Mean (95% CI)	**Vigabatrin Powder** Mean (95% CI)	**p-value**
Dose Accuracy	Dose Delivered (mg)	1115 mg (1105-1125 mg)	1010 mg (941-1083 mg)	p<0.01
	% Target Dose Delivered	99% (98-100%)	90% (84-96%)	p<0.01
Dose Variability	Difference in Dose from Target (mg)	12 mg (7-19 mg)	122 mg (82-183 mg)	p<0.0001
	% Difference in Dose from Target	0.6% (0.2-1.5%)	9.7% (5.9-16.1%)	p<0.0001
Dose Volume	% mL difference from target	1.5% (1.1-2.0%)	1.8% (1.1-2.9%)	p=0.56

Target dose, 1125 mg; Target volume VGB-RTU solution, 11.25 mL; Target volume vigabatrin powder, 22.5 mL
Statistical comparisons were adjusted, while controlling for caregiver experience

(target range 1013–1238 mg) was 30/30 (100%) for VGB-RTU solution (1073–1154 mg; −4.6% to +2.6%); whereas only 23/30 (77%) successfully administered similar doses of vigabatrin using vigabatrin powder (425–1390 mg; −62.2 to +23.6%). Furthermore, approximately 70% of VGB-RTU solution doses deviated by <2% from the target dose; versus only 20% of the vigabatrin powder doses ($p < 0.001$). Remarkably, while no VGB-RTU solution calculated dose deviated by 5% or more from the target dose, 56.7% of the vigabatrin powder doses did ($p < 0.0001$). For vigabatrin powder, 23.4% of doses provided for vigabatrin powder deviated >10% relative to the target dose (Fig. 2).

Statistical analysis after log-transformation revealed that on average subjects delivering VGB-RTU solution achieved a calculated dose of 1115 mg (95% confidence interval (CI) 1105–1125 mg), while those preparing vigabatrin powder achieved 1010 mg (95% CI 941–1083 mg), $p < 0.01$. Similarly, caregivers

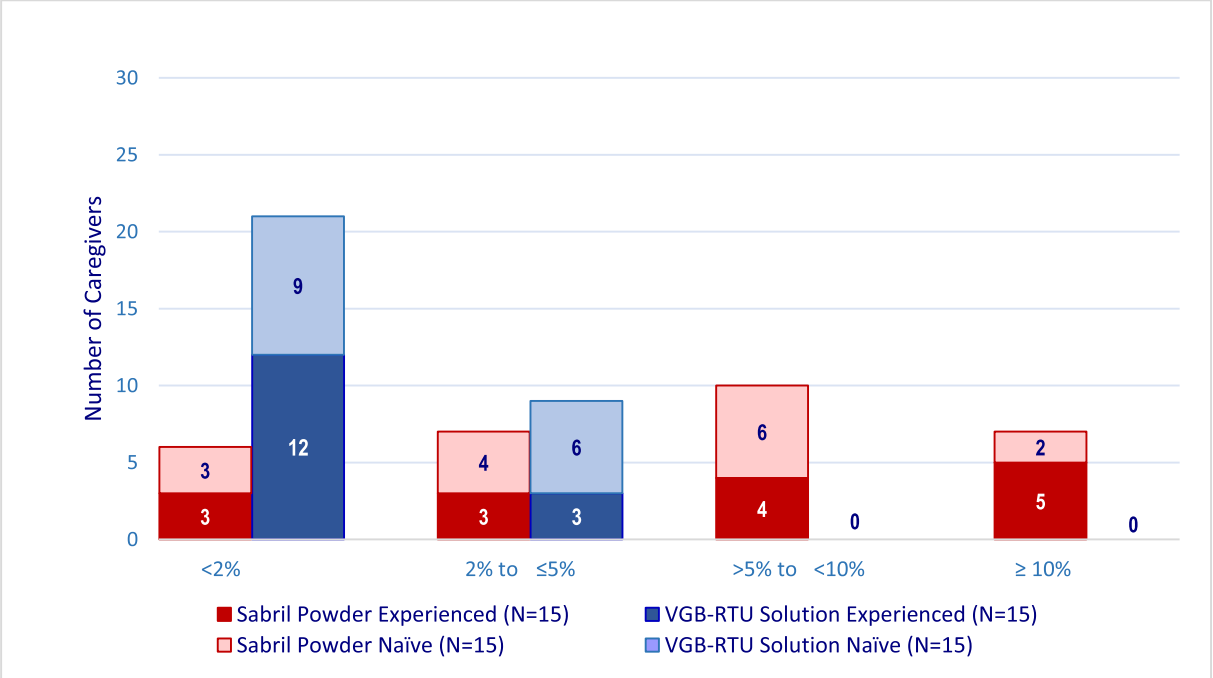

Fig. 2 Deviation of dose administered relative to intended dose ($N = 30$ participants; 15 experienced; 15 naïve)

preparing VGB-RTU solution achieved on average 99% of the percent target dose delivered (95% CI 98–100%). This result was statistically higher when compared to vigabatrin powder preparations which averaged 90% of the percent target dose delivered (95% CI 84–96%), $p < 0.01$.

Controlling for caregiver experience, the overall adjusted difference in dose from the 1125-mg target dose for VGB-RTU solution was 12 mg (95% CI 7–19 mg), compared to vigabatrin powder with 122 mg (95% CI 82–183 mg). This resulted in a statistically significant difference as prepared vigabatrin powder doses averaged 110 mg lower than doses of VGB-RTU solution ($p < 0.0001$) regardless of caregiver experience. Statistical differences in dosing were also found as a result of caregiver experience within the model that included treatment groups ($p = 0.03$). Naïve caregivers provided doses closer to the target dose than experienced caregivers, while controlling for treatment group.

On average, while controlling for caregiver experience, caregivers dosing VGB-RTU solution were within 0.6% (95% CI 0.2–1.5%) of the target dose, while those preparing vigabatrin powder were within 9.7% (95% CI 5.9–16.1%), $p < 0.0001$. A comparison of these averages reveals that vigabatrin powder doses exhibit a 9.1% greater difference from target than VGB-RTU solution doses ($p < 0.0001$).

On average, all users delivered volumes within 2% of the specified amount for both products. The difference in milliliters dosed compared to the target for caregivers preparing VGB-RTU solution averaged 1.5% (95% CI 1.1–2.0%), while vigabatrin powder achieved an average difference of 1.8% (95% CI 1.1–2.9%), $p = 0.56$. Thus, there is no statistically significant difference in milliliter percent difference from target between VGB-RTU solution and vigabatrin powder. The lack of significance is important as it clarifies that the point of failure is unrelated to the ability of the users to deliver the prescribed volume of solution.

DISCUSSION

This study, despite the small sample size, identified statistically significant differences in the

ability of 30 participants to successfully prepare and administer a ready-to-use solution and a medication requiring the end-user to reconstitute a solution from a commercially available powder prior to each dose.

All participants using VGB-RTU solution administered a calculated dose within ± 5% of the target; while only 77% of participants using vigabatrin powder administered a dose within ± 10% of the target. After log-transformation, the average VGB-RTU solution dose administered exhibited < 1% accuracy difference from the target; whereas the average dose of vigabatrin powder exhibited a 7.9% difference. These averages provide a general indication of a caregiver's ability to prepare and administer a prescribed dose of vigabatrin without direct instruction from a healthcare professional, and demonstrate that doses of VGB-RTU solution were more accurate than doses from vigabatrin powder.

It is notable that bivariate analysis determined that the raw data for vigabatrin powder was non-normally distributed and required log-transformation prior to statistical analyses for accuracy and variability. Similar skewed results were not seen for VGB-RTU solution; however, since log transformation was required to properly perform vigabatrin powder statistical analysis, it was performed on both data sets. This statistical treatment preferentially minimized gross dosage errors generated by caregivers for vigabatrin powder doses.

The variability of doses for VGB-RTU solution was shown to be significantly lower than for solutions prepared from vigabatrin powder, indicating that participants were more consistently able to provide the prescribed dose of VGB-RTU solution.

Differences in administered doses were shown to be related to the ability of the caregiver to prepare solutions at the proper vigabatrin concentration in accordance with labeled directions, rather than in their ability to deliver the prescribed volume of solution.

FDA-approved vigabatrin labeling allows for only a short trial to allow the clinician to determine whether vigabatrin can provide a baby with clinically meaningful seizure treatment. This narrow trial window makes it imperative that the baby receives the dose intended by the physician every time.

Changes in the preparation regimen of vigabatrin powder such as differing numbers of packets, differing reconstitution volumes, and different dosage volumes can make it difficult for caregivers to reliably deliver the prescribed dose of VGB when using a vigabatrin powder versus a ready-to-use liquid, such as VIGAFYDE™.

No statistically significant difference was noted in the ability of experienced and naïve users to successfully deliver the prescribed volume of reconstituted solutions of vigabatrin powder or VGB-RTU solution. This finding confirms that the point of failure is related to the ability of the caregivers to prepare solutions containing the correct concentration of vigabatrin, rather than in their ability to deliver the correct dosage volume.

Since no reconstitution is required prior to using the ready-to-use vigabatrin oral solution, the dose delivered is not dependent on the ability of the caregiver to properly prepare a 50 mg/mL vigabatrin solution.

Limitations

Although VGB is dosed chronically, this study did not evaluate caregiver preparation of multiple doses of the same medication.

HPLC analysis was not performed on the VGB-RTU solution since, unlike reconstituted solutions of vigabatrin, the dose of the VGB-RTU solution could be calculated on the basis of the volume dispensed. Only blinded reconstituted vigabatrin powder samples (interspersed with blinded control samples) were provided to the testing laboratory.

The study was insufficiently powered to identify differences between experienced and naïve caregivers, or between male and female caregivers.

In this study, caregivers preparing the doses received written instructions only and were unable to ask clarifying questions about dose preparation. This guidance was not consistent with the approved labeling for vigabatrin powder.

CONCLUSION

Despite the small sample size, this study identified statistically significant differences in the ability of naïve and experienced caregivers to successfully prepare and administer a single dose of a ready-to-use vigabatrin solution and a commercially available vigabatrin powder. VGB-RTU solution doses exhibited superior accuracy ($p \leq 0.01$) and less variability ($p \leq 0.0001$) compared to reconstituted vigabatrin powder doses.

This study showed that the use of a ready-to-use vigabatrin oral solution was associated with fewer errors in delivering the desired dose since vigabatrin powder for oral solution was subject to reconstitution errors by caregivers during preparation.

The use of a ready-to-use solution supports the ability of the caregiver to provide consistent and correct doses of vigabatrin.

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Author Contributions. Conceptualization: Raenel Gibson; Study Design and Methodology: Raenel Gibson and Ron Klima; Formal analysis, Investigation, Original manuscript writing, review, and editing: Raenel Gibson, Jay Van Horn, and Ron Klima; All authors read and approved the final manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. The authors, Raenel Gibson, Jay Van Horn, and Ron Klima were employed by Pyros Pharmaceuticals, Incorporated at the time of the study. Insight by Nemera received reimbursement for the conduct of this study. Alcami Corporation received reimbursement for conducting HPLC method validation and HPLC vigabatrin analyses of samples and control samples. Tedor Pharma, Incorporated received reimbursement for the following activities: control sample preparation, sample weight collection, aliquot preparation, and sample blinding. Precision AQ™ received reimbursement for statistical analysis.

Ethical Approval. This nonclinical study was approved by a national Institutional Review Board, Castle IRB (Chesterfield, MO). The investigation was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments, and was consistent with Good Clinical Practice and applicable regulatory requirements. Informed consent was obtained from participants prior to performing any study-related procedures.

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