Pharmacokinetics of Intravenous Lorazepam in Pediatric Patients with and without Status Epilepticus

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Objective To evaluate the single dose pharmacokinetics of an intravenous dose of lorazepam in pediatric patients treated for status epilepticus (SE) or with a history of SE.

Study design Ten hospitals in the Pediatric Emergency Care Applied Research Network enlisted patients 3 months to 17 years with convulsive SE (status cohort) or for a traditional pharmacokinetics study (elective cohort). Sparse sampling was used for the status cohort, and intensive sampling was used for the elective cohort. Non-compartmental analyses were performed on the elective cohort, and served to nest compartmental population pharmacokinetics analysis for both cohorts.

Results A total of 48 patients in the status cohort and 15 patients in the elective cohort were enrolled. Median age was 7 years, 2 months. The population pharmacokinetics parameters were: clearance, 1.2 mL/min/kg; half-life, 16.8 hours; and volume of distribution, 1.5 L/kg. On the basis of the pharmacokinetics model, a 0.1 mg/kg dose is expected to achieve concentrations of approximately 100 ng/mL and maintain concentrations >30 to 50 ng/mL for 6 to 12 hours. A second dose of 0.05 mg/kg would achieve desired therapeutic serum levels for approximately 12 hours without excessive sedation. Age-dependent dosing is not necessary beyond using a maximum initial dose of 4 mg.

Conclusions Lorazepam pharmacokinetics in convulsive SE is similar to earlier pharmacokinetics measured in pediatric patients with cancer, except for longer half-life, and similar to adult pharmacokinetics parameters except for increased clearance. (J Pediatr 2012;160:667-72).

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CL Clearance
Vdss Steady state volume of distribution
ED Emergency department
NC Non-compartmental
SE Status epilepticus
T1/2 Half-life
T1/2 Beta Elimination half-life

It is estimated that 4 to 8 children per 1000 will experience an episode of status epilepticus (SE) before age 15 years.1 Benzodiazepines are the most effective agents for the initial treatment of SE, achieving lasting control in 80% of patients.2,3 Textbooks and expert opinion recommend both diazepam and lorazepam as initial therapy for children in SE and provide recommended doses that are commonly used in practice.4,5 In addition, midazolam has been used for initial therapy6,7 or for refractory status.8,9 Many experts support the use of lorazepam rather than diazepam as initial therapy for pediatric SE although diazepam is approved by the US Food and Drug Administration and lorazepam is not.10,11 Increased duration of action, increased effectiveness, and a lower incidence of respiratory depression have been cited as potential advantages of lorazepam compared with diazepam.12,13 The limited pediatric data available indicate that lorazepam metabolism in children may differ from adult patients.14,15 In addition, SE itself may alter pharmacokinetics, and children with SE may be receiving other anticonvulsant medications that may affect lorazepam metabolism. Data are needed to determine the unique pharmacology of lorazepam in children with SE.
We conducted a prospective multi-center study to evaluate the pharmacokinetics of a single intravenous dose of lorazepam in children. Patients were enrolled at 10 sites of the Pediatric Emergency Care Applied Research Network, which was founded in 2001 by the Emergency Medical Services for Children program to help overcome barriers to pediatric emergency medicine research. The study was approved by the institutional review boards of the participating hospitals.

The status cohort included patients who came to the emergency department (ED) in SE and received lorazepam as part of standard medical care. The status cohort patients were further categorized in patients who had pre-consented to participate in the study before their presentation in SE (cohort 1a), and patients who came to the ED in SE and consented to participate in the study after they had received lorazepam (cohort 1b). Pre-consented patients were identified from neurology practices and EDs and had a history of recurrent ED visits for SE.

The elective cohort included patients with a history of seizures who electively received one dose of lorazepam in a scheduled pharmacokinetic study in a clinical research center.

Patients between the ages of 3 months and 17 years were eligible. We excluded patients with pregnancy, sustained hypotension, significant dysrhythmia, known lorazepam allergy, anemia, history of using lorazepam within 4 days of dosing, weight <8 kg because of the volume of blood sampling required, and patients for whom we could not obtain blood samples.

Patients in the status cohort received 0.05 to 0.1 mg/kg of lorazepam, depending on treating physician preference, to a maximum of 4 mg, and patients in the elective cohort received 0.05 mg/kg to a maximum dose of 2 mg. For both cohorts, lorazepam was withdrawn from the manufacturer’s refrigerated vial in a syringe just before slow intravenous push for 1 minute. For the status cohort, additional medications for the treatment of SE were administered at the discretion of the treating physician, including additional doses of lorazepam. Vital signs were recorded every 15 minutes for 1 hour after dosing and less frequently thereafter. At each vital sign interval, notation was made about the need for assisted ventilation during the earlier period. The Riker sedation-agitation scale was recorded at specified intervals because lorazepam may cause either sedation or agitation. A modified Riker score was created for preverbal subjects and was validated in a separate study (K.M. Brown, unpublished data). Adverse events were reported in accordance with federal regulations.

Status cohort subjects had as many as 5 pharmacokinetic samples for total lorazepam lorazepam-glucuronide concentrations collected between 0 and 48 hours after administration of study drug. Elective cohort subjects had as many as 13 pharmacokinetic samples collected from 0 to 48 hours. Larger sample volumes were required for free (unbound) drug concentration determination and therefore were measured at only two to 3 time points. Blood was sampled from a second intravenous site located on a different extremity from the site where lorazepam was administered. Blood was collected in 2-mL sodium heparin tubes; serum was separated and immediately frozen, then shipped in monthly batches on dry ice for analysis.

Separate analytical methods were developed for the analysis of total lorazepam, unconjugated lorazepam (protein bound + unbound), and unbound (free) lorazepam. The unconjugated lorazepam plasma concentrations were initially determined with a high performance liquid chromatographic with ultraviolet detection method. This assay was linear between 20 and 2000 ng/mL. After the initial samples, we determined that a more sensitive method was needed. The liquid chromatography/mass spectroscopy method we developed and used to measure the remaining unconjugated lorazepam samples gave lower limits of quantitation at 1 ng/mL for both the unconjugated and the unbound drug and at 2 ng/mL for total drug. Results generated with each method were reported separately for data analysis. Assay performance characteristics are available from the authors on request. Unbound lorazepam concentrations were determined with ultrafiltration. Total lorazepam concentrations (molar normalized) were determined with enzymatic cleavage of the glucuronide from the lorazepam metabolite with beta glucuronidase before extraction and analysis. The lorazepam glucuronide concentrations were determined by subtracting the concentration of unconjugated lorazepam from the total lorazepam concentration.

Analyses
The analyses included both intensive non-compartmental (NC) and population pharmacokinetic evaluations. NC analyses are used to describe pharmacokinetics without making assumptions about how the drug is distributed and eliminated. The NC analyses were performed on data from the elective cohort, and served to nest the compartmental population pharmacokinetic analysis for both cohorts.

In the NC analysis, the area under the plasma drug concentration versus time curve was determined using the linear trapezoidal rule up to the final measurable concentration point and the area under the curve after the final measurable
concentration ($C_{\text{last}}$) estimated as $C_{\text{last}}/\lambda_z$, in which $\lambda_z$ is the negative slope of the natural log concentration compared with the time profile. Total body clearance of lorazepam was determined with the formula: $\text{Dose}/\text{area under the plasma drug concentration versus time curve. The volume of distribution was calculated from the equation: } \text{Vdss} = \frac{\text{Dose} \times \text{AUMC}}{\text{area under the curve}}, \text{ in which AUMC is the area under the first moment curve.}$

The population pharmacokinetic analysis was performed with data from both cohorts by using the computer software NONMEM (version VI; ICON, Ellicott City, Maryland). Structurally, a two-compartment model with first order elimination (ADVAN3) was evaluated. Pharmacokinetic parameters were scaled by subject size before evaluation of other potential co-variates. An allometric approach to size was used scaling subject weight to the 0.75 power (weight$^{0.75}$) for clearance ($\text{CL}$) and weight to 1.0 power (weight$^{1.0}$) for volume of distribution.²⁰ Allometric scaling is a common approach to account for size in pharmacokinetic (and biologic) modeling. It is more robust than linear weight in accounting for size (ie, liver and renal function), but does not account for maturational changes and other developmental differences. The potential impact of clinical co-variates on pharmacokinetic parameters was evaluated in a two-stage approach. Potential co-variates that were evaluated included age, sex, albumin level, liver enzymes, ethnicity, study cohort, and concomitant medications.

Co-variates were retained in the final pharmacokinetic model when they improved the goodness of fit statistically (decrease in minimum objective function by >8, $P < 0.05$). The lorazepam population pharmacokinetic model was further expanded to include modeling of lorazepam glucuronide disposition to improve the pharmacokinetic model. The appropriateness of the final models with and without metabolites was evaluated with a bootstrap method (Wings for NONMEM; http://wfn.sourceforge.net) with 1000 iterations.

Empiric Bayesian estimates of individual lorazepam pharmacokinetic parameters were generated from the final model with the post hoc subroutine. Group comparison from the individual Bayesian parameters were performed with Pearson correlation co-efficients and Wilcoxon rank sum tests. A $P$ value <.05 was considered significant.

The free fraction of lorazepam was determined in each subject as the free lorazepam concentration divided by total lorazepam concentration. The impact of lorazepam concentration, age, albumin, and concomitant medications on free fraction was assessed with a general linear models approach. We were also specifically interested in whether recent seizure activity altered the proportion of free lorazepam compared with the proportion in the elective cohort.

We used the model to predict peak serum levels and the duration of maintenance of therapeutic serum levels. In the absence of pharmacodynamic data, we used pharmacokinetic data from the literature to estimate that serum levels between 30 and 100 ng/mL are expected to provide anticonvulsant effects without producing levels associated with excessive sedation.²¹⁻²³

### Results

Sixty-nine patients received study medication, of whom 6 discontinued participation because of withdrawal of consent or technical difficulties with intravenous access. Thus, 63 patients had samples for pharmacokinetic analysis (Table I); 15 patients were enrolled in the elective cohort, and 48 patients were enrolled in the status cohort. Patients ranged in age from 5 months to 17 years, with a median age of 7 years, 2 months.

In the status cohort, 36 patients received a single dose, with a mean dose of 1.7 mg (0.08 mg/kg). Eight patients (16.7%) required a second dose of lorazepam within 30 minutes, with a mean total dose of 2.4 mg (0.13 mg/kg), and 4 patients (8.3%) received 3 or more doses (total mean dose, 5.3 mg, 0.16 mg/kg) within 30 minutes. Six patients (12.5%) required crossover to another medication within 30 minutes of initial lorazepam dosing. Three patients (6.3%) required endotracheal intubation. One patient required assisted ventilation without intubation, and one patient required insertion of a nasal airway. Other adverse reactions within 1 hour of dosing included hypotension ($n = 13$), extreme sedation ($n = 8$), vomiting ($n = 5$), tachycardia ($n = 7$), and agitation ($n = 3$). Two patients (4.2%) had suspected aspiration. We could not determine whether these adverse events were caused by lorazepam or by the underlying SE. The total mean lorazepam dose was higher in the patients with adverse events than in patients without ($0.12 \pm 0.06$ versus $0.08 \pm 0.04$, $P = .03$). In the elective cohort, the only adverse event was agitation in one patient.

### Pharmacokinetics

Table II summarizes the NC pharmacokinetic evaluation for the elective cohort. Eight pharmacokinetic samples (0.3%) were excluded, 7 because of suspected contamination from the infused drug and one because of collection during the lorazepam infusion. Overall, the mean area-under-the-curve to infinity was 822.5 ng·hr/mL, and the median area-under-the-curve to infinity was 601.5 ng·hr/mL with an average dose of 0.04 mg/kg. The overall fit of the population pharmacokinetic model was good for the wide range of individuals in the population. There were no co-variates meeting criteria for inclusion into the model. Thirty-three subjects (23 in the status cohort, 10 in the elective cohort) had received, at baseline, at least one agent that can induce drug-metabolizing enzymes. The calculated value for terminal (beta) $T_{1/2}$ was 16 hours for a typical 24-kg child. The empiric Bayesian estimated parameters from the post-hoc analysis are summarized in Table III. The model demonstrated good model prediction of observed concentrations even when applied to the patients exhibiting...
the highest and lowest individual CLs and in a patient who received a total of 9 doses of lorazepam during the pharmacokinetic sampling interval.

The typical population pharmacokinetic parameters estimates were: \( CL = 0.14 \text{ L/hr/kg}^{0.75}, \) \( V_c = 0.91 \text{ (L/kg)}; \) \( V_{dss} = 1.37 \text{ L/kg}; \) and \( Q = 1.05 \text{ L/hr/kg}^{0.75}. \) Overall, lorazepam pharmacokinetic post-hoc parameters from the population analysis were as follows: \( CL = 1.2 \text{ (mL/min/kg)}; \) \( V_{dss} = 1.48 \text{ L/kg}; \) and half-life \( (T_{1/2}) = 16.8 \text{ hr} \) (Table III). The free-fraction was determined in 109 of 343 samples and averaged 10.2% \( \pm 5.8\%. \) Free fraction was independent of lorazepam concentration and cohort, and there was no apparent age effect. The ratio of lorazepam-glucuronide/lorazepam concentrations averaged 0.99 and increased throughout the sampling time \( (r = 0.59, P < .001). \) The NC analysis generated consistent findings to the population-based approach with a slightly lower estimate for CL \( (0.057 \text{ L/hr/kg}) \) because of the older average age of patients in the elective cohort. The median CL and Vdss from the bootstrap analysis were identical to the values generated from the original dataset with 95% CIs of 0.12 to 0.16 L/hr/kg \( ^{0.75} \) for CL and 1.25 to 1.58 L/kg for Vdss.

There were potentially modest age effects seen in CL and Vdss when normalized to weight; however, age-associated changes in lorazepam CL did not meet criteria for inclusion in the final pharmacokinetic model with allometric scaling, nor when scaled by body surface area. The impact of age on volume of distribution was the most powerful co-variate in univariate analyses; however, this also failed to meet criteria for inclusion in the final pharmacokinetic model. Additionally, because both CL and Vdss trended toward larger values in younger patients, the combined potential age-effect impact on CL and Vdss countered each other, with the net result of no age effect on \( T_{1/2}. \)

On the basis of the final pharmacokinetic model derived from this study, a dose of 0.1 mg/kg with a maximum 4 mg is expected to achieve near-peak concentrations of approximately 100 ng/mL and maintain concentrations >30 to 50 ng/mL for 6 to 12 hours in the typical pediatric patient. A second dose of 0.1 mg/kg would potentially achieve maximal concentrations that are too high for the desired clinical effects, whereas a second dose of 0.05 mg/kg (maximum 2 mg) would achieve desired therapeutic serum levels for approximately 12 hours (Figure). Although some age effects were seen in this model, it is not anticipated that this would necessitate age-dependent dosing beyond the truncation of dosing at 40 kg \( (\text{ie, maximum single dose of } 4 \text{ mg}). \) When repeated doses of lorazepam are required for maintenance therapy as an inpatient, for example, then dosing should occur at least every 12 hours to prevent fluctuations in concentration more than two-fold.

### Discussion

This study evaluated lorazepam pharmacokinetics in children with SE. One of the challenges to gaining US Food and Drug Administration approval for this indication has been the inability to study lorazepam pharmacokinetics and efficacy in the emergency setting. We were able to measure population pharmacokinetics with sparse sampling and compartmental modeling in pediatric patients with SE, augmented by intensive NC modeling in an elective cohort of subjects.

The use of a population-based approach in this study provided flexibility in sample collection time and dosing necessary to determine pharmacokinetics during active SE. For example, early pharmacokinetic samples were not possible in most patients with SE. This approach also allowed use of lorazepam-glucuronide concentrations to provide additional information on lorazepam metabolism, thus improving the precision of the CL estimates. Although there was more than a 20-fold range in lorazepam CL, we did not find any significant differences in lorazepam elimination from

<table>
<thead>
<tr>
<th>Table I. Study enrollment</th>
<th>Age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months to &lt;3 years</td>
</tr>
<tr>
<td>Patients screened</td>
<td>52</td>
</tr>
<tr>
<td>Ineligible or refused consent</td>
<td>32</td>
</tr>
<tr>
<td>Enrolled</td>
<td>20</td>
</tr>
<tr>
<td>Status cohort</td>
<td>19</td>
</tr>
<tr>
<td>Elective cohort</td>
<td>1</td>
</tr>
<tr>
<td>Pharmacokinetic data obtained</td>
<td>18</td>
</tr>
<tr>
<td>Completed 30-day follow-up</td>
<td>16</td>
</tr>
</tbody>
</table>

| Table II. NC pharmacokinetic parameters from elective cohort patients |
|----------------|---------|---------|---------|---------|---------|---------|
| Cmax (ng/mL)  | 15      | 15      | 15      | 15      | 15      | 15      |
| AUC0-\(\infty\) | 29.3-209.6 | 253.3-3202.5 | 3.3-131.50 | 5.5-67.5 | 0.33-4.05 | 9.5-47.0 |
| CL (mL/min/kg) | 56.1 ± 44.9 | 822.5 ± 706.1 | 49.33 ± 30.83 | 31.95 ± 13.99 | 1.92 ± 0.84 | 20.5 ± 10.2 |
| Vdz (L/kg)    | 42.2    | 601.5   | 41.50   | 32.34   | 1.94    | 18.1    |
| \(T_{1/2}\) (hours) | 42.2    | 601.5   | 41.50   | 32.34   | 1.94    | 18.1    |

\(C_{max}\), maximum concentration; \(AUC_{0-\infty}\), area-under-the-curve to infinity; \(Vdz\), apparent volume of distribution.
patients with active seizures compared to those with an elective pharmacokinetic evaluation. In addition, protein binding was not different in the two cohorts. None of the common anticonvulsant medications were associated with alterations in lorazepam elimination.

The age-related changes in lorazepam CL, scaled allometrically, did not reach the pre-defined level needed for inclusion in the final population pharmacokinetic model. Glucuronidation by the liver increases early during infancy and may exceed adult capacity in young children because of the larger relative liver size. In this study, there were only 5 subjects <1 year of age, and all of them were >4 months of age. This modest number of infants, the large inter-subject variability, and the developmental changes in lorazepam CL. However, when lorazepam CL was modeled with raw weight (weight1.0), it was greater in infants and younger children than adolescents. Our results are consistent with earlier literature on uridine 5'-diphospho-glucuronosyltransferase metabolism, demonstrating marked increases in the neonatal period but only modest changes in UDP-glucuronosyltransferase activity after 6 months of age.24,25

In adult studies, the average lorazepam CL ranges from 0.75 to 1.28 mL/min/kg, and the T1/2 Beta ranges from 9 to 22 hours (Table IV; available at www.jpeds.com).26-33 Taking the adult experience as a whole, lorazepam CL in our patients was approximately 20% higher than in adults, and the T1/2 Beta was approximately equal to that in adults. The average lorazepam CL in this study is consistent with studies in pediatric patients with cancer between 2 to 12 years of age, although this study had a longer T1/2 (15.0 hours versus 10.5 hours). This difference may be related to the longer sampling duration in this study.

Overall, lorazepam was successful in treating SE. Of the 48 patients with SE, 42 (87.5%; 95% CI, 74.8%-95.3%) were successfully treated with one or two doses; only 6 of 48 patients required a third dose of an anticonvulsant medication within 30 minutes. Four of 48 patients with SE (8.3%; 95% CI, 2.3%-20.0%) required assisted ventilation for respiratory depression; in one patient, this was transient. Although this study was not designed to test the efficacy and safety of lorazepam for pediatric SE, our results are consistent with earlier pediatric studies demonstrating successful treatment in 65% to 81% of patients34-36 and respiratory depression in 4% to 27% of patients.37

The pediatric lorazepam pharmacokinetic parameters are within the range previously reported in adults and CL similar to that previously reported in pediatric patients with cancer. Weight-adjusted CL and Vdss tended to be higher in infants and younger children compared with older children; however, ability in lorazepam CL, and use of allometric scaling to approximate for liver size limited the ability to detect developmental changes in lorazepam CL. However, the average lorazepam CL ranges from 0.75 to 1.28 mL/min/kg, and the T1/2 Beta ranges from 9 to 22 hours (Table IV; available at www.jpeds.com).26-33 Taking the adult experience as a whole, lorazepam CL in our patients was approximately 20% higher than in adults, and the T1/2 Beta was approximately equal to that in adults. The average lorazepam CL in this study is consistent with studies in pediatric patients with cancer between 2 to 12 years of age, although this study had a longer T1/2 (15.0 hours versus 10.5 hours). This difference may be related to the longer sampling duration in this study.

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the magnitude of these differences was not statistically significant. Concomitant medications or enzyme-inducing anticonvulsant medications did not affect lorazepam CL. SE did not affect lorazepam protein binding and CL compared with subjects without SE. These pharmacokinetic results, with safety and tolerability data, indicate that a dose of 0.1 mg/kg (4 mg maximum) will achieve and maintain lorazepam concentrations in the range associated with anticonvulsant effects for 6 to 12 hours and would not exceed those associated with heavy sedation. When a second dose of lorazepam is required for SE, a dose of 0.05 mg/kg (2 mg maximum) will result in serum levels associated with anticonvulsant activity for approximately 12 hours without achieving levels associated with excessive sedation.

References

Appendix

Table IV. Data from adult studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dose</th>
<th>n</th>
<th>CL (mL/min/kg)</th>
<th>Vd (L/kg)</th>
<th>% Unbound</th>
<th>T1/2(hours)</th>
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<tbody>
<tr>
<td>Greenblatt 1977</td>
<td>5 mg</td>
<td>4</td>
<td>0.75</td>
<td>0.84</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Kraus 1978</td>
<td>2 mg</td>
<td>11</td>
<td>1.28</td>
<td>1.28</td>
<td>6.8%</td>
<td>22</td>
</tr>
<tr>
<td>Greenblatt 1979</td>
<td>2-3 mg</td>
<td>15</td>
<td>0.99</td>
<td>1.11</td>
<td>10.0%</td>
<td>14</td>
</tr>
<tr>
<td>Patwardhan 1980</td>
<td>2 mg</td>
<td>8</td>
<td>0.92</td>
<td>1.63</td>
<td>7.7%</td>
<td>21</td>
</tr>
<tr>
<td>Wermeling 2001</td>
<td>2 mg</td>
<td>11</td>
<td>1.02</td>
<td>1.32</td>
<td></td>
<td>16.6</td>
</tr>
<tr>
<td>Crem 1991</td>
<td>0.3 mg/kg</td>
<td>10</td>
<td>1.02</td>
<td>0.78</td>
<td>8.4%</td>
<td>9</td>
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<tr>
<td>Weighted average</td>
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<td>59</td>
<td>1.03</td>
<td>1.20</td>
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<tr>
<td>Package insert</td>
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<td>1.1 ± 0.4</td>
<td>1.3</td>
<td>8.8%</td>
<td>14.5 ± 5</td>
</tr>
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</table>

Vd, volume distribution.