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A Pilot Study Assessing Pharmacokinetics and Tolerability of Oral and Intravenous Baclofen in Healthy Adult Volunteers

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Abstract

Our objective was to characterize baclofen pharmacokinetics and safety given orally and intravenously. Twelve healthy subjects were enrolled in a randomized, open-label, crossover study and received single doses of baclofen: 3 or 5 mg given intravenously and 5 or 10 mg taken orally with a 48-hour washout. Blood samples for baclofen analysis were collected pre-dose and at regular intervals up to 24 hours post-dose. Clinical response was assessed by sedation scores, ataxia, and nystagmus. Mean absolute bioavailability of oral baclofen was 74%. Dose-adjusted areas under the curve between the oral and intravenous arms were statistically different ($P = .0024$), whereas area under the curve variability was similar (coefficient of variation: 18%-24%). Adverse effects were mild in severity and not related to either dose or route of administration. Three- and 5-mg intravenous doses of baclofen were well tolerated. Seventy-four percent oral bioavailability indicates that smaller doses of intravenous baclofen are needed to attain comparable total drug exposures.

Keywords

muscle spasticity, baclofen, intravenous therapy, baclofen withdrawal, pharmacokinetics

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Spasticity is a frequent and prominent symptom of upper motor neuron injury in individuals with cerebral palsy, multiple sclerosis, acquired spinal cord injury, brain injury, and neurodegenerative disorders.[1-3] In general, spasticity develops when an imbalance occurs in the excitatory and inhibitory input to α motor neurons; this imbalance is caused by damage to the central nervous system. Baclofen is a drug used to treat spasticity. It is structurally similar to γ-aminobutyric acid (GABA) and acts as a $GABA_B$ agonist at the level of the spinal cord.[4] Baclofen is available as oral and intrathecal formulations. The intrathecal formulation is used in conjunction with an implanted programmable pump to provide a constant infusion of the drug. Individuals treated with oral or intrathecal may experience a withdrawal syndrome if it is abruptly discontinued. Interruption in intrathecal therapy may be the result of problems with the programmable pump or catheter. Interruption in oral baclofen therapy may be the result of illness resulting in inability to take oral medications, noncompliance, or a scheduled surgery for which patients must temporarily stop taking oral medications. This withdrawal syndrome can be quite severe, resulting in a rebound increase in muscle tone and spasms, status epilepticus, hallucinations, and a neuromalignant syndrome–like picture potentially resulting in rhabdomyolysis and multisystem organ failure.[3,5-10]

The current recommended management of baclofen withdrawal is inadequate. In the case of interruption of intrathecal therapy, attempts to replace the medication with oral baclofen require large doses in an effort to control withdrawal symptoms.[6,11] Moreover, in spite of using large doses, symptoms are not controlled completely and adverse effects including sedation, nausea, vomiting, and dizziness may occur. Diazepam is used by most clinicians for its antispasticity effect and to decrease the likelihood of acute seizures; however, it could result in sedation and respiratory depression.[6,12] In conditions such as ileus or gastroenteritis, baclofen is not absorbed when given orally and can result

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in baclofen withdrawal. Use of an intravenous baclofen formulation could prevent or minimize the complications in individuals in whom oral or intrathecal drug delivery is interrupted. Intravenous administration of baclofen would permit rapid attainment of drug concentrations as well as accurate and precise dose titration, thus allowing for more expeditious treatment of withdrawal symptoms and reduced risk of adverse effects.

Although oral and intrathecal baclofen have been used for decades, safety and pharmacokinetic studies of intravenous baclofen in humans have not been published. Moreover, although there are several reports of intravenous baclofen administration in both animals and humans,[13-16] details of the formulation used in these studies and pharmacokinetic results were not reported. In addition, very limited information was provided about the dose selection and adverse events in these studies. Because a US Food and Drug Administration (FDA)–approved intravenous formulation of baclofen is not currently available, a recent clinical study in patients used an extemporaneously compounded sterile formulation of baclofen (2.5 mg/mL, pH 6.6) to reduce pain from muscle spasm and migraines (J Krusz, personal communication, 2013). In the current clinical investigation, a commercially available intrathecal formulation of baclofen (Lioresal Intrathecal, 2 mg/mL; Novartis Pharmaceuticals) was used.

These circumstances suggest that a FDA-approved commercial intravenous baclofen product would enhance management of patients with spasticity. The first step in the development of such a product is demonstration of its safety in an animal model. Therefore, a pilot study in dogs was conducted to assess the bioavailability, short-term safety, and tolerance of intravenous baclofen in comparison to oral administration. Subsequently, intravenous baclofen at doses of 0.5 to 3 mg/kg was found to be well tolerated in dogs.[17] The next phase in the development of an intravenous baclofen formulation would be to conduct a series of investigations in humans. In the current study, safety, tolerability, and pharmacokinetics of an intravenous formulation of baclofen has been evaluated and compared with oral administration. The primary objective of this study was to characterize baclofen pharmacokinetics after oral and intravenous administration in healthy volunteers under fasted conditions in order to determine dosing of intravenous baclofen in subsequent studies. The other objective of this study was to assess the safety and tolerability of a single dose of baclofen given intravenously.

Methods

Participants

Twelve healthy adult volunteers gave informed consent and were compensated for participation. Participants who were pregnant or lactating, had a history of sensitivity to intravenous drug administration, or who had a history of significant diseases were excluded from the study. All female volunteers involved in the study were postmenopausal for 1 year, surgically incapable of bearing children, or were practicing at least 1 approved method of contraception. The volunteers were medication free for 48 hours before, during, and 24 hours after the administration of the study drug. The study was approved by the institutional review board of the University of Minnesota and was conducted at the PRISM clinical research unit in St. Paul, MN. The principal investigator was present at the clinical research unit during drug administration.

Study Drugs and Design

The study utilized a randomized, open-label, 2-way crossover design to compare the pharmacokinetics and bioavailability of the oral tablet with an intravenous formulation in 12 healthy participants. The oral formulation used in this study was a commercially available 10 mg tablet (10 mg baclofen, Qualitest Pharmaceuticals). For administering the 5-mg oral dose in the initial 3 patients, the tablets were cut in half. A single intravenous dose of either 3 or 5 mg was administered over 15 minutes, using the commercially available 2 mg/mL intrathecal baclofen formulation (Lioresal Intrathecal) that is used in baclofen pumps. Initially, 3 participants received single 3-mg intravenous and 5-mg oral doses on separate study days with at least a 48-hour washout period between doses. After assessing the safety and clinical tolerance of intravenous baclofen for the 3 initial participants, an additional 9 participants received a 5-mg intravenous dose and a 10-mg oral dose of baclofen after a washout period of at least 2 days. Blood samples (6 mL) for the measurement of plasma concentrations of baclofen were collected in blood collection tubes containing K_2 ethylenediaminetetraacetic acid at the following times: prior to dosing; at 5, 15, and 30 minutes; and at 1, 2, 4, 6, 8, 10, 12, and 24 hours after drug administration. Plasma was separated by centrifugation and stored frozen until analysis.

Drug Assay

Study plasma samples were prepared by adding 50 μL of a 500 ng/mL levetiracetam solution (internal standard) to 250 μL of K_2 ethylenediaminetetraacetic acid human plasma. Baclofen and internal standard were extracted from plasma by precipitating protein with methanol and dried under nitrogen at approximately 40°C. The dried residues were reconstituted in 300 μL of mobile phase consisting of 20 mM ammonium acetate–methanol (75:25) solution. After 1 minute of vortex mixing, reconstituted sample solution was filtered and injected onto the high-performance liquid chromatograph–mass spectrometer system. Standard curve samples over a range of 20 to 400 ng/mL baclofen and quality control samples containing 30 (low), 80 (medium), and 240 ng/mL (high) baclofen were prepared and analyzed in triplicate along with the study samples. The assay was linear over the range 20–400 ng/mL with a lower limit of quantification of 20 ng/mL.

Data Analysis

Baclofen concentration–time data were analyzed using a noncompartmental pharmacokinetic approach with Phoenix software (version 6.2; Pharsight Corporation, Mountain View, CA). The terminal rate constant (λz) was determined from the slope of the terminal log-linear portion of the plasma concentration–time curve, and the terminal half-life ($t_{1/2}$) was calculated as $\ln 2/(\lambda z)$. Maximum plasma concentrations (C_{max}) and time to maximum concentration (T_{max}) were determined by direct observation of the data. The area under the concentration–time curve to the last nonzero plasma concentration (C_{last}) that was above half the lower limit of quantification (10 ng/mL) was calculated by the trapezoidal rule and reported as AUC_{last}. The area under the concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{last} + (C_{last}/\lambda z)$. Mean and standard deviation values for the parameters were also obtained using the descriptive statistics

Table 1. Mean ± SD of Baclofen Pharmacokinetic Parameters Following Oral (10 mg) and Intravenous (5 mg) Administration.

Pharmacokinetic parameter	5 mg IV (mean[a] ± SD)	10 mg oral (mean ± SD)
C_{max} (ng/mL)	310 ± 74	174 ± 16
T_{max} (h)[b]	–	1.0 (0.5-2.0)
AUC_{last} (ng·h/mL)	593 ± 111	878 ± 199
$AUC_{0-\infty}$ (ng·h/mL)	707 ± 166	1023 ± 232
$AUC_{0-\infty}$/Dose[c] (ng·h/mL/mg)	141 ± 33	102 ± 23
Bioavailability (%)	–	74 ± 15
$T_{1/2}$ (h)	4.52 ± 1.6	4.03 ± 0.73

Abbreviations: AUC, area under the curve; IV, intravenous; SD, standard deviation.
[a]Mean values are presented as arithmetic means.
[b]Median (min, max) reported for T_{max}.
[c]Two-tailed *P* value < .05 (paired t-test performed on dose-normalized area under the curve).

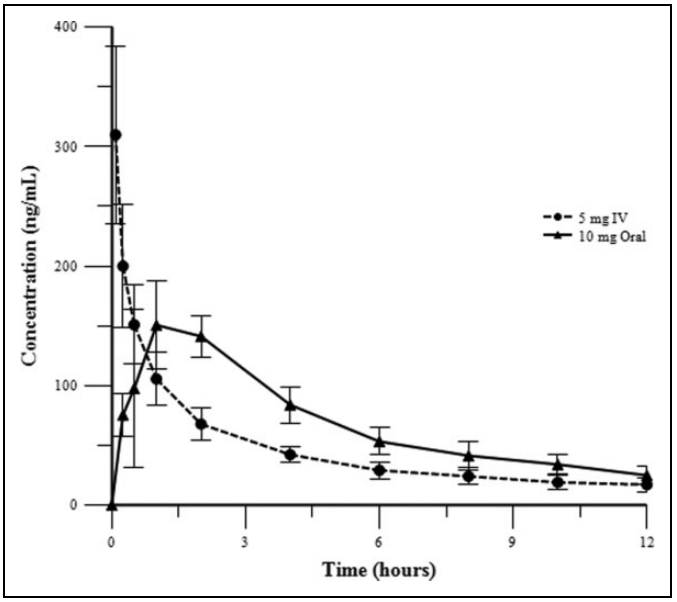

Figure 1. Mean (±standard deviation) plasma concentration–time profiles of baclofen after intravenous and oral administration (0-12 hours).

tool in Phoenix version 6.2. A paired t-test was used to determine if statistical differences existed in log normalized, dose-adjusted area under the curve between oral and intravenous arms.

Safety Evaluation

Safety was assessed by electrocardiography (ECG) results, blood pressure and pulse monitoring, assessment of central nervous system toxicity, injection site irritation, side effects and tolerability, as well as physical examinations at 12 and 24 hours after the drug administration. Ataxia assessment by observation of gait was done prior to drug administration, every 30 minutes for the first 4 hours, and at 12 and 24 hours after the drug administration. At the same time as ataxia assessments, nystagmus and sedation were also assessed. Nystagmus was assessed both at neutral and lateral gaze. Sedation was assessed using the Stanford Sleepiness Scale (SSS) given below[18]:

1 = Feeling active, vital, alert, or wide awake
2 = Functioning at high levels, but not at peak; able to concentrate
3 = Awake, but relaxed; responsive but not fully alert
4 = Somewhat foggy, let down
5 = Foggy; losing interest in remaining awake; slowed down
6 = Sleepy, woozy, fighting sleep; prefer to lie down
7 = No longer fighting sleep, sleep onset soon; having dream-like thoughts

Results

All 12 subjects (9 male and 3 female) completed the study. The mean (±standard deviation) weight of the 12 patients was 79.6 (±13.5) kg. The age range of subjects was 26 to 56 years, with a mean age of 39.3 years.

A summary of the pharmacokinetic parameters is presented in Table 1. A valid estimate of λz could not be calculated in subjects receiving the 3-mg intravenous dose, and thus $AUC_{0-\infty}$ and $t_{1/2}$ were not reported. This was either due to a coefficient of determination (r^2) <0.9000, or an extrapolated area under the curve that was >30% of $AUC_{0-\infty}$. The mean concentration-time profiles for both (5 mg intravenous and 10 mg oral) arms are shown in Figure 1. When the subjects received the intravenous formulation, the observed maximum baclofen concentration occurred at the 5-minute time point, whereas the median T_{max} for oral administration was 1 hour. The mean (standard deviation) C_{max} values for the oral (10 mg) and intravenous (5 mg) doses were 176 (15) ng/mL and 313 (75) ng/mL, respectively (Figure 1). The mean $t_{1/2}$ was similar for both the oral and intravenous arms (4 and 4.52 hours, respectively). The mean absolute bioavailability of the oral baclofen tablets (Table 1) was 74%. There was a significant difference in log-normalized, dose-adjusted area under the curves ($P = .0024$) between oral and intravenous dosing with similar variability (coefficient of variation: 18%-24%).

The investigational intravenous formulation was well tolerated. Most common adverse events were somnolence, mild ataxia, and mild nystagmus. One subject had mild end point nystagmus at baseline and following oral and intravenous baclofen. Two other subjects had mild nystagmus, one after intravenous and one after oral baclofen. Mild somnolence (Stanford Sleepiness Scale score ≤ 4) was observed with both the intravenous (7 subjects) and oral (3 subjects) doses. Mild ataxia was noted following administration of intravenous baclofen (4 subjects) and oral baclofen (7 subjects). All treatment-emergent adverse events were characterized by the investigator as being mild in severity, and all subjects returned to their baseline values within 6 hours of drug administration. All subjects were able to normally communicate and walk without assistance throughout the entire period of the observation. No adverse event met the criteria to be serious, and none resulted in a subject's withdrawal from the study.

Discussion

To our knowledge, this is the first-in-humans study investigating intravenous baclofen safety and pharmacokinetics in comparison with oral baclofen. Adverse effects were mild in severity and were not related to route of administration. All subjects in both oral and intravenous groups were awake; however, ''fogginess'' was reported in both groups. Non-drug-related factors possibly confounded sedation scores. For instance, one subject worked the night shift prior to a study day and was sleep deprived, which could have resulted in a higher sedation score. All subjects could walk without assistance, although mild ataxia was observed in both groups. However, very low doses were used in this study; tolerability at higher clinical doses remains to be established.

Absolute oral baclofen bioavailability is 74%, indicating that approximately 25% of a 10-mg dose is either not absorbed or undergoes first-pass metabolism prior to drug reaching systemic circulation. It also implies that a smaller intravenous baclofen dose will be needed when substituted for oral doses. For example, assuming linear kinetics, the total systemic exposure (area under the curve) after an intravenous dose of 15 mg would be equivalent to the total exposure achieved after 20 mg of oral baclofen dose. However, the assumption of linear pharmacokinetics needs to be evaluated in a dose-escalation study before one can confidently use the 25% reduction to determine the intravenous dose that results in comparable total drug exposure as an oral dose. One of the key findings of this study was that the between-subject variability in exposure (area under the curve) was similar in both intravenous and oral arms (coefficient of variation: 18%-24%). Variability estimates gained from this study will be helpful in determining the sample size required for future dose-escalation trials.

The results of this study indicate that the C_{max} observed following intravenous administration would be about 4 times higher than observed with a similar oral dose. Generally when medications are given intravenously, a higher C_{max} could be a safety and tolerability concern. However, in our studies with an animal model, there was no toxicity seen at 0.5 mg/kg intravenous doses ($\sim$10-12.5 mg) of baclofen in dogs despite C_{max} values in the range of 1000 to 1500 ng/mL. The dose escalation study in the dogs demonstrated that higher single doses of 2 and 3 mg/kg ($\sim$38-75 mg total dose) eventually resulted in toxicity, but the onset was delayed by 2 to 3 hours after peak concentrations, which ranged from 4000 to 7000 ng/mL,[17] further emphasizing the need for a dose escalation study in humans. The disconnect between peak plasma concentrations and drug effects was also demonstrated in a mouse model.[19] Moreover, delayed toxicity implies that clinicians might need to wait a sufficiently long time period ($\sim$2-3 hours) to see the maximum clinical effect of an intravenous baclofen dose in humans as well.

The results of this study differ somewhat from previously published pharmacokinetic studies of oral baclofen given to healthy subjects.[20-22] Kowalski et al[20] reported an average peak concentration of 540 ng/mL in 18 healthy volunteers who received a 25-mg dose. Assuming linear kinetics, a 10 mg oral dose would result in a peak concentration of approximately 215 ng/mL. However, in the present investigation, the average peak concentration was 176 ng/mL following a 10-mg oral dose. Average T_{max} and half-life reported by Kowalski et al was 2.79 and 6.54 hours, respectively, both of which are longer than those reported herein (1 and $\sim$4 hours, respectively). Differences in peak concentrations could be due to differences in the dissolution or disintegration of tablets, saturable absorption mechanisms at higher doses, assay methodology, or blood sampling times.

Intravenous baclofen could be useful in several clinical scenarios including prevention or treatment of withdrawal from oral or intrathecal baclofen. One such scenario would be to use as a bridge therapy when oral baclofen is discontinued for any reason. Another scenario would use intravenous baclofen when intrathecal therapy is interrupted because of pump failure or infection leading to removal of pump. Intravenous baclofen could also be used to treat baclofen withdrawal. Finding the correct intravenous doses would be difficult when substituting intrathecal doses, as knowledge of bioavailability is not directly relevant. Moreover, it has been shown that there is no correlation between the intrathecal dosage infused and the corresponding cerebrospinal fluid baclofen concentration, which further complicates the calculation of therapeutic intravenous doses in managing withdrawal resulting from intrathecal discontinuation.[23] Designing and conducting a study to determine equivalency of intravenous to intrathecal dosing would be challenging because of both ethical and technical concerns. For these reasons, studies in appropriate animal models may be informative but are lacking.

Conclusion

The pharmacokinetic data gained from this study will guide the design of future trials directed at the development of intravenous baclofen for bridge therapy. Dose escalation studies are needed to assess the safety of higher clinically relevant doses as well as determining the linearity of exposure at higher oral doses to aid in correct calculation of replacement intravenous doses. Once the safety and pharmacokinetics of higher intravenous doses is demonstrated, dose substitution studies in patients on chronic oral baclofen therapy will be necessary to assess multidose safety and pharmacokinetics. Lastly, clinicians should be aware of the potential cost of intravenous baclofen therapy. Nevertheless, in view of the lack of satisfactory alternatives, severity of the withdrawal signs and symptoms as well as the possible complications, the costs could be justified and would probably be part of inpatient hospital billing.

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Author Contributions

All authors except MHT contributed to study design, data collection, and analysis of data. SKA, RLK, MHT, and LEK wrote the manuscript and JCC, LDC, and LAS reviewed it.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: LEK is a consultant for Medtronic Inc, the supplier of Lioresal Intrathecal.

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Ethical Approval

The study was approved by the Institutional Review Board of the University of Minnesota. IRB committee approval number is 1206M15625.

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