Population Pharmacokinetics of Oral Baclofen in Pediatric Patients with Cerebral Palsy

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Objective To characterize the population pharmacokinetics (PK) of oral baclofen and assess impact of patient-specific covariates in children with cerebral palsy (CP) in order to support its clinical use.

Subjects design Children (2-17 years of age) with CP received a dose of titrated oral baclofen from 2.5 mg 3 times a day to a maximum tolerated dose of up to 20 mg 4 times a day. PK sampling followed titration of 10-12 weeks. Serial R- and S-baclofen plasma concentrations were measured for up to 16 hours in 49 subjects. Population PK modeling was performed using NONMEM 7.1 (ICON PLC; Ellicott City, Maryland).

Results R- and S-baclofen showed identical concentration-time profiles. Both baclofen enantiomers exhibited linear and dose/kg-proportional PK, and no sex differences were observed. Average baclofen terminal half-life was 4.5 hours. A 2-compartment PK model with linear elimination and transit absorption steps adequately described concentration-time profiles of both baclofen enantiomers. The mean population estimate of apparent clearance/F was 0.273 L/h/kg with 33.4% inter-individual variability (IIV), and the apparent volume of distribution (V_{ss}/F) was 1.16 L/kg with 43.9% IIV. Delayed absorption was expressed by a mean transit time of 0.389 hours with 83.7% IIV. Body weight, a possible genetic factor, and age were determinants of apparent clearance in these children.

Conclusion The PK of oral baclofen exhibited dose-proportionality and were adequately described by a 2-compartment model. Our population PK findings suggest that baclofen dosage can be based on body weight (2 mg/kg per day) and the current baclofen dose escalation strategy is appropriate in the treatment of children with CP older than 2 years of age. *(J Pediatr 2014;164:1181-8)*.

Baclofen is one of the skeletal muscle relaxants for the treatment of spasticity of cerebral palsy (CP) in adults. It is an agonist for gamma-aminobutyric acid B receptors on both pre- and post-synaptic neurons in spinal cord and brain.[1] Baclofen binding to gamma-aminobutyric acid receptors may reduce release of excitatory neurotransmitters in pre-synaptic neurons and stimulate inhibitory neuronal signals in the post-synaptic neurons.[2] Oral baclofen has been used to treat spasticity in children for more than 3 decades,[3] although clinical results do not show consistent effectiveness.[3,4] Careful dose titration is recommended until symptomatic effect is attained and possible side effects are minimized.

AUC_τ	Area under the curve within the dosing interval	PG	Pharmacogenomics
BS	Bootstrap	PK	Pharmacokinetics
CL	Clearance	PopPK	Population pharmacokinetics
CL_{CR}	Creatinine clearance	SNP	Single-nucleotide polymorphism
CP	Cerebral palsy	SVPC	Standardized visual predictive check
GAGE	Gestational age	QID	4 times a day
GERD	Gastroesophageal reflux disease	TID	3 times a day
IIV	Inter-individual variability	TDOS	Total daily dose
MTT	Mean transit time	WTKG	Body weight in kg
NCA	Noncompartmental analysis		

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Baclofen is rapidly and extensively absorbed following oral administration, with bioavailability of 70%-85%. It is primarily eliminated by renal excretion in unchanged form (renal clearance: 10-17 L/h). Large inter-individual variability (IIV) (over 90%) has been observed in both oral absorption and elimination processes.[5,6] Safety and efficacy of oral baclofen are well documented for adults in the drug package insert. However, there is little information on the pharmacokinetics (PK) properties of baclofen in children. Establishment of safe and effective dosing strategies for children with CP is needed.

This study investigated the PK properties of baclofen in children with CP and sought subject-specific properties that may influence PK profiles and clinical responses among pediatric patients. The concentration-time profiles of baclofen in these children were obtained after dose titration. The PK properties of both R- and S-baclofen were characterized using population modeling methods.

Methods

Subjects with spastic CP (n = 61; age 2-17 years) were enrolled after attainment of institutional review board approval at 9 sites as part of the National Institute of Child Health and Human Development-2005-13-2 protocol. Enrollment was monitored to ensure approximately even representation of sex and age groups. Eligible subjects had a Gross Motor Function Classification Scale level of II-V, leg hypertonia/spasticity defined as an Ashworth Scale score of at least 2, and a Tardieu score of 2 (spastic catch) in at least 1 knee (flexors and/or extensors). Eligibility criteria precluded subjects with active intrathecal baclofen pump within the past 6 months, use of baclofen and other tone-modifying agents within the past 4 months, non-medically prescribed drug abuse, alcohol/tobacco use, and use of enzyme inducers or drugs known to alter renal function. Subjects were also excluded if they had severe gastroesophageal reflux disease (GERD) including prior biopsy or endoscopy proven esophagitis or a history of vomiting more than 3 times per week, delayed gastric emptying, malnutrition, renal or liver disease, severe respiratory or cardiac disease, and uncontrolled seizures.

This was an open-label, ascending dose study of oral baclofen in pediatric subjects with spastic CP. The range of doses and escalation strategies used for this study were based on current clinical practices and preliminary data. Subjects under age 6 years did not receive dosages above 10 mg 3 times a day (TID). Otherwise, the maximum dosage was 20 mg 4 times a day (QID). Three formulations were used: 2 mg/mL liquid solution (UPM Pharmaceuticals, Baltimore, Maryland), 5 mg tablets (Novartis Pharmaceuticals, Basel, Switzerland), and 10 mg tablets (Qualitest Pharmaceuticals, Huntsville, Alabama). The first 15 subjects started the study on the liquid preparation, but only 2 were still on liquid baclofen at the time of the PK visit. Eight (of 15) switched to the tablets during dose escalation and provided PK samples.

All subjects started on oral baclofen at 2.5 mg TID and received an increased dose every 2 weeks until they reached either the maximum tolerated dose or the maximum study dosage. The first dose was given at approximately 7 a.m. The TID and QID regimens involved unequal dosing intervals of 7/7/10 and 5/5/5/9 hours. Doses were given at least 30 minutes before or at least 2 hours after a meal. The 2-week interval between each dose escalation was chosen to reduce the risk for side effects and to allow transient side effects to resolve. Subjects who could not tolerate at least 5 mg TID were discontinued from the study with a baclofen tapering process.

One pre-dose and 13 post-dose blood samples were collected serially over 16 hours after the second daily dose during a PK visit that occurred at the maximum tolerated dose or maximum dose limit (80 mg/d). The subsequent scheduled doses were not given until the PK sampling period was completed. R- and S-baclofen were measured in plasma, using a validated tandem mass spectrometry method (**Appendix**; available at www.jpeds.com).

PK Modeling Analysis

Figure 1 (available at www.jpeds.com) depicts the subject array and disposition during the baclofen dosing period and PK analysis process. The PK of oral baclofen was analyzed with a mixed-effects population model, incorporating intra-individual variability and IIV. A 2-compartment model with first-order absorption and elimination was used as the base model (**Figure 2**; available at www.jpeds.com) after evaluation of various PK model candidates based on the NONMEM objective functions and weighted residual plots. The absorption process was modeled by chained transit steps that describe delayed absorption during multiple dosing[7,8] with an assumption that absorption is completed within each dosing interval. IIV, represented by Eta, was estimated using an exponential variability model for clearance (CL), the volume of the central compartment (V_c), the absorption rate into plasma (k_a), mean transit time (MTT), and number of absorption transit steps (n). Log-normal distribution was assumed for the PK variables. The unidentified residual variability was modeled with a combination of additive and proportional errors. An empirical Bayes estimate of Eta for each PK variable was obtained from the base model. Covariate analysis was then performed by visually exploring the graphs (Eta-plots) of IIV versus patient-specific characteristics, including body weight in kg (WTKG), age, gestational age (GAGE), birth body weight, sex, race, serum creatinine concentration, creatinine clearance (CL_{CR}), bladder or kidney function, gastric motility/gastroesophageal reflux status, and disease severity status. A preliminary pharmacogenomics (PG) analysis was performed to explore the impact of genetic variation on PK variables. Potential covariates were subsequently evaluated using a model fitting procedure. The details of structural model equations, variability models, covariate assessment, and exploratory PG analysis are presented in the **Appendix**.

Model Assessment

It has been reported that R-baclofen is pharmacologically active, although both baclofen enantiomers can bind to the