Pharmacokinetics and bioequivalence of a liquid formulation of hydroxyurea in children with sickle cell anemia.

Jeremie H. Estepp
Chiara Melloni
Courtney D. Thornburg
Paweł Wiczling
Zora Rogers

See next page for additional authors

Follow this and additional works at: https://scholarlyexchange.childrensmercy.org/papers

Part of the Hematology Commons, Hemic and Lymphatic Diseases Commons, Pediatrics Commons, and the Pharmaceutical Preparations Commons

Recommended Citation

This Article is brought to you for free and open access by SHARE @ Children's Mercy. It has been accepted for inclusion in Manuscripts, Articles, Book Chapters and Other Papers by an authorized administrator of SHARE @ Children's Mercy. For more information, please contact library@cmh.edu.
Creator(s)
Jeremie H. Estepp, Chiara Melloni, Courtney D. Thornburg, Paweł Wiczling, Zora Rogers, Jennifer A. Rothman, Nancy S. Green, Robert Liem, Amanda M. Brandow, Shelley E. Crary, Thomas H. Howard, Maurine H. Morris, Andrew Lewandowski, Uttam Garg, William J. Jusko, Kathleen A. Neville, and Best Pharmaceuticals for Children Act-Pediatric Trials Network Administrative Core Committee

This article is available at SHARE @ Children's Mercy: https://scholarlyexchange.childrensmercy.org/papers/297
Pharmacokinetics and Bioequivalence of a Liquid Formulation of Hydroxyurea in Children With Sickle Cell Anemia

Jeremie H. Estepp, MD, Chiara Melloni, MD, Courtney D. Thornburg, MD, MS, Pawel Wiczling, PhD, Zora Rogers, MD, Jennifer A. Rothman, MD, Nancy S. Green, MD, Robert Liem, MD, MS, Amanda M. Brandow, DO, MS, Shelley E. Crary, MD, MS, Thomas H. Howard, MD, Maurine H. Morris, BA, Andrew Lewandowski, PhD, Uttam Garg, PhD, William J. Jusko, PhD, and Kathleen A. Neville, MD, MS on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network Administrative Core Committee

Departments of Hematology and Pathology, St. Jude Children’s Research Hospital, Memphis, TN, USA 2Division of Clinical Pharmacology, Department of Medicine, Duke University Medical Center, Durham, NC, USA 3Department of Pediatrics, University of California-San Diego, La Jolla, CA, USA 4Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdańsk, Gdańsk, Poland 5Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA 6Division of Pediatric Hematology/Oncology, Duke University Medical Center, Durham, NC, USA 7Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation, Columbia University Medical Center, New York, NY, USA 8Division of Hematology, Oncology, and Stem Cell Transplant, Ann & Robert H. Lurie Children’s Hospital of Chicago, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA 9Section of Pediatric Hematology/Oncology, Medical College of Wisconsin, and Children’s Research Institute of the Children’s Hospital of Wisconsin, Milwaukee, WI, USA 10Division of Pediatric Hematology–Oncology, University of Arkansas for Medical Sciences/

Corresponding Author: Kathleen A. Neville, MD, MS, Section of Pharmacology and Toxicology, Arkansas Children’s Hospital, 1 Children’s Way, Little Rock, AR 72202 ; Email: kaneville@uams.edu

ClinicalTrials.gov identifier: NCT01506544

Author Contributions
J.H.E. enrolled participants, analyzed the results, and wrote the manuscript; C.M. designed and executed the protocol and provided critical review and editing of manuscript; C.D.T. enrolled participants and provided critical review and editing of manuscript; P.W. analyzed results and provided critical review and editing of manuscript; Z.R. contributed to protocol design, enrolled participants, and provided critical review and editing of manuscript; J.A.R., N.S.G., R.L., A.M.B., S.E.C., and T.H.H. enrolled participants and provided critical review and editing of manuscript; M.H.M. designed and executed the protocol and provided critical review and editing of manuscript; A.L. designed the protocol, analyzed results, and provided critical review and editing of manuscript; U.G. designed the protocol, analyzed samples, and provided critical review and editing of manuscript; W.J.J. contributed to the overall research design and protocol design, analyzed results, and critically reviewed and edited the manuscript; K.A.N. contributed to the overall research design and protocol design, served as study chair and IND holder, executed the protocol, analyzed results, and wrote the manuscript.

Conflict-of-Interest Disclosures
Jeremie H. Estepp receives funding support from Daiichi Sankyo and Eli Lilly and Co. Courtney D. Thornburg has research funding from MAST Pharmaceuticals for sickle-cell-related research; she also received NIH funding for the BABY HUG follow-up studies. Zora Rogers has received honoraria and consultation work from Apopharma, Baxter, Roche, and GSK as well as from the Texas Department of State Health Services. Shelley E. Crary has served on the advisory board for hemophilia for Grifols. The other authors have no potential conflicts to report.

Supporting Information
Additional supporting information may be found in the online version of this article at the publisher’s web-site
Arkansas Children’s Hospital, Little Rock, AR, USA 11 Division of Pediatric Hematology and Oncology, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA 12 Duke Clinical Research Institute, Durham, NC, USA 13 The Emes Corporation, Rockville, MD, USA 14 Department of Pathology and Laboratory Medicine, Children’s Mercy Hospitals and Clinics, Kansas City, MO, USA 15 Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, Buffalo, NY, USA 16 Section of Pharmacology and Toxicology, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, USA

Abstract

Hydroxyurea (HU) is a crucial therapy for children with sickle cell anemia, but its off-label use is a barrier to widespread acceptance. We found HU exposure is not significantly altered by liquid vs capsule formulation, and weight-based dosing schemes provide consistent exposure. HU is recommended for all children starting as young as 9 months of age with sickle cell anemia (SCA; HbSS and HbSβ0thalassemia); however, a paucity of pediatric data exists regarding the pharmacokinetics (PK) or the exposure-response relationship of HU. This trial aimed to characterize the PK of HU in children and to evaluate and compare the bioavailability of a liquid vs capsule formulation. This multicenter, prospective, open-label trial enrolled 39 children with SCA who provided 682 plasma samples for PK analysis following administration of HU. Noncompartmental and population PK models are described. We report that liquid and capsule formulations of HU are bioequivalent; weight-based dosing schemes provide consistent drug exposure; and age-based dosing schemes are unnecessary. These data support the use of liquid HU in children unable to swallow capsules and in those whose weight precludes the use of fixed capsule formulations. Taken with existing safety and efficacy literature; these findings should encourage the use of HU across the spectrum of age and weight in children with SCA; and they should facilitate the expanded use of HU as recommended in the National Heart; Lung; and Blood Institute guidelines for individuals with SCA.

Keywords

bioequivalent; hydroxyurea; children; sickle cell anemia

Sickle cell anemia (SCA; HbSS and HbSβ0thalassemia) is a chronic, debilitating, and costly disease affecting an estimated 100,000 individuals in the United States. 1 Hydroxyurea (HU), a ribonucleotide reductase inhibitor, is a potent fetal hemoglobin inducer and antisickling agent. In 1998, HU received approval by the US Food and Drug Administration (FDA) for adults with SCA, largely based on data generated from the Multicenter Study of Hydroxyurea in Patients with Sickle Cell Anemia (MSH) trial (NCT00000586). The MSH trial showed that HU was safe and significantly decreases the incidence of pain, acute chest syndrome, hospitalization, and transfusion in adults with severe SCA. 2

An estimated 36,000 children (<19 years old) suffer from SCA in the United States. 1 Since its approval for adult usage, HU has been prescribed off-label for children with SCA to ameliorate their disease, and the laboratory and clinical benefits in children parallel those
seen in adults with reductions in pain, acute chest syndrome, hospitalizations, and transfusion requirements. In September 2014, an expert panel selected by the National Heart, Lung, and Blood Institute (NHLBI) released evidence-based management guidelines for sickle cell disease. Included in these guidelines was a “strong recommendation” for children ≥9 to ≤2 months of age and a “moderate recommendation” for children >42 months of age to be offered HU therapy to reduce complications related to SCA.

Despite supporting data and recommendations, pediatric use continues to be off-label. FDA approval requires additional pharmacokinetic (PK) information to include a pediatric indication on the label for HU and approve it for pediatric use. Although efficacy and toxicity profiles of HU in children with SCA have been favorable, limited data exist regarding the PK or exposure-response relationship. The FDA offered a written request under the Best Pharmaceuticals for Children Act (BPCA) to specifically address this knowledge gap and highlighted the need for PK data to compare liquid to capsule formulations.

In response to this written request, the “Pharmacokinetics and Bioavailability of a Liquid Formulation of Hydroxyurea in Pediatric Patients with Sickle Cell Anemia” trial (NCT01506544) was designed to characterize the disposition of a liquid HU formulation in a cohort of toddlers (≥2 to ≤5 years). This study had two hypotheses: (1) the PK in toddlers administered a liquid formulation would not differ significantly from that observed in older children; and (2) the PK profile of the liquid formulation would not differ significantly from the PK profile of a proprietary capsule formulation.

Methods

Study Population

Following approval from each local center’s institutional review board, children ≥2 to ≤7 years of age were recruited from 7 medical centers in the United States. Eligible participants had either HbSS or HbSβ0 thalassemia. The inclusion criteria included being in a “well” state (ie, no acute SCA manifestations or other acute illness), weight of ≥10 kg, body mass index (BMI) ≥5th and ≤95th percentiles, and normal hepatic, renal, and gastrointestinal function. Children were ineligible if they had a malignancy, had received a recent blood transfusion, or had cytopenia noted on screening laboratory assessment. Additionally, children were excluded for concomitant medication usage that could potentially affect the analysis (Tables S1 and S2). Of note, 90% (n = 35/39) of children were actively being treated with HU.

Study Design

This was a prospective, open-label, trial composed of 2 arms that assessed the PK parameters of HU administered under direct supervision. Participants were allowed only clear liquids from 6 hours to 1 hour prior to HU administration, and they abstained from food or drink 1 hour before and 1 hour following drug administration. A regular age-appropriate diet was resumed 2 hours after dosing. In arm 1, toddlers (≥2 to ≤5 years) (n = 17) received a single dose of a standardized liquid formulation of HU (100 mg/mL). In arm
2, children (>5 to ≤17 years) (n = 22) received each standardized formulation (liquid and capsule) on separate occasions in a randomized, crossover fashion. The second dose was administered between 24 hours and 10 days following the initial dose. Following all HU dosing, blood PK samples were collected predose and then at 10, 15, 30, 45, and 60 minutes, and 1.5, 2, 4, 6, and 8 hours postdose in both arms. To ensure balanced enrollment, arm 1 was subdivided into ages 2–3 years and 4–5 years, and arm 2 was divided into ages 6–11 years and 12–17 years.

Investigational Products

Hydroxyurea USP was purchased from a commercial pharmaceutical company and reconstituted with a commercially available cherry syrup diluent to a final concentration of 100 mg/mL at each site’s investigational pharmacy. Droxia® capsules (200 mg) were purchased and supplied to study sites without modification or disturbance of the commercially obtained bottles. Capsules were administered whole and were not opened. Children received HU at a dose of either 20 mg/kg if they were HU naive or their normal daily dosage (rounded to the nearest 200 mg and no greater than 30 mg/kg) for children currently prescribed HU therapy.

Bioanalytical Methods

Whole blood (1 mL) was collected into heparinized tubes, inverted a minimum of 8 to 10 times, placed immediately on ice, and centrifuged at 750g for 10 minutes at 4°C. Plasma was then stored at −70°C until shipped to Children’s Mercy Hospital, where it was analyzed. PK samples were analyzed using a validated gas chromatography-mass spectrometry (GC-MS) technique that was linear from 0.1 to 100 μg/mL of HU.

The intra- and interassay coefficients of variation (CV) were consistently <10% across concentrations spanning the range of linearity.

Bioavailability and a Noncompartmental PK Method

A noncompartmental PK analysis was performed using WinNonlin software (Certera, Princeton, New Jersey). All PK parameters were expressed with descriptive statistics of arithmetic mean, standard deviation (SD), and coefficient of variation (CV%).

The assessment of bioavailability followed FDA guidelines. The geometric least-squares (LS) means of the maximum observed plasma concentration (Cmax), the area under the concentration-vs-time curve calculated using the log-linear trapezoidal method from time 0 to the last quantifiable concentration (AUClast), and the area under the concentration-vs-time curve calculated using the log-linear trapezoidal method from time 0 extrapolated to time infinity (AUC∞) were generated using WinNonlin. The ratio of these parameters for liquid: capsule and their 90% confidence limits were also obtained using WinNonlin. The paired t-test used to compare Cmax, AUClast, AUC∞, and time to maximum plasma concentration (Tmax) and the assessment of mean (SD; range) was calculated using Microsoft Excel 2007.
Population Pharmacokinetic Models

A 1-compartment model with absorption described by a series of transit compartments was fitted to the concentration-time profiles of HU using the following equations:

\[
\frac{dA}{dt} = \text{Input}(t) - \frac{CL}{V} A, \quad A(0) = 0 \quad (1)
\]

where \( A \) is the amount of HU in the central compartment, \( CL \) is the systemic clearance, \( V \) is the volume of distribution, \( F \) is the fraction of the dose absorbed, plasma concentrations \( (C_p) = A/V \), and \( \text{Input}(t) \) denotes the input rate of HU into the central compartment:

\[
\text{Input}(t) = \sum_{k=1}^{2} I(\text{Dose}_k, (t-TOD_k)) \quad (2)
\]

where \( t \) is the time since the first dose, \( \text{Dose}_k \) denotes the dose given at \( k \)th visit (occasion) at time \( \text{TOD}_k \), and \( I(x,y) \) is the individual input function defined as:

\[
I(x,y) = \begin{cases} 
    F \cdot x \cdot k_{tr} \cdot \frac{(k_{tr} \cdot y)^{N-1} \cdot e^{-k_{tr} \cdot y}}{N!} & \text{for } y > 0 \\
    0 & \text{for } y \leq 0
\end{cases} \quad (3)
\]

where \( k_{tr} \) is the first-order transit rate constant equal to \((N+1)/\text{MTT}\); MTT (mean transit time) corresponds to the average time spent by a molecule traveling from the distal to the central compartment (average absorption time), and \( N \) is number of transit compartments. The actual parameters generated were \( CL/F \) and \( V/F \) due to uncertain bioavailability. Equations 1–3 allow for joint estimation of the number of compartments and MTT.

Interindividual variability (IIV) represented by \( \eta \) and interoccasion variability (IOV) represented by \( \kappa \) were modeled assuming the log normal distribution. Model fitting and covariate analysis were performed using NONMEM software (version 7.2.0, Icon Development Solutions, Ellicott City, Maryland) as described in the supplemental materials.

Allometric Scaling

The effect of body size on the volume and clearance parameters was predicated on allometric principles with theoretical exponents as follows:

\[
V_{ik} = \theta_V \left( \frac{BW_{ik}}{70} \right)^{0.75} \exp(\eta_{V,i} + \kappa_{V,k}) \quad (4)
\]

\[
CL_{ik} = \theta_{CL} \left( \frac{BW_{ik}}{70} \right)^{0.75} \exp(\eta_{CL,i} + \kappa_{CL,k}) \quad (5)
\]

where \( V_i \) and \( CL_i \) denote the individual values of volume and clearance; \( \theta_V \) and \( \theta_{CL} \) are the population (typical) estimates of volume and clearance, \( BW_{i,k} \) is the individual body weight on the \( k \)th occasion (visit), and 70 is the body weight (kg) of a standard adult. This approach facilitated the comparison of PK parameters with adult data.
Covariance Analysis

Relationships between patient-specific covariates (such as age, sex, height, alkaline phosphate, alanine transaminase, aspartate transaminase, direct bilirubin, blood urine nitrogen, creatinine, glucose, potassium, sodium, and sickle cell genotype) and the empirical Bayes estimates of η and κ for each PK parameter were sought by plotting individual estimates of η and κ against tested covariates to identify their influence. Potential relationships were subsequently evaluated using nonlinear mixed-effect modeling with the stepwise forward inclusion ($P < .05$) and backward elimination ($P < .005$) method. Further details regarding covariate assessment are provided in the supplemental materials.

Results

In total, 39 participants enrolled. In arm 1, 94% (n = 16/17) of young children (n = 6, aged 2–3 years; n = 10, aged 4–5 years) received study drug. All 16 children completed the study and are included in the PK and safety analyses. In arm 2, 25 children were enrolled, and 92% (n = 23; 12 aged 6–11 years, 11 aged 12–17 years) received study drug and are included in the PK and safety analyses. For the bioavailability analysis of participants in arm 2, 96% of children (n = 22) completed both PK visits, with 48% (n = 11) receiving capsule formulation first. One participant voluntarily withdrew from the second PK analysis due to loss of intravenous access. The PK samples obtained with the study drug (liquid formulation) during this child's first PK visit were analyzed in the PK and safety analysis. Table 1 summarizes demographic, baseline laboratory parameters, and HU dose by study arm and participant age.

Bioavailability

The PK of liquid (n = 22) and capsule (n = 22) formulations were similar (Table 2). Figure 1 shows HU concentration-vs-time profiles in 4 representative children who received both liquid and capsule formulations. Both formulations were rapidly absorbed with a mean (SD) $T_{\text{max}}$ of 0.86 (0.53) hours and resulted in a $C_{\text{max}}$ of 33.8 (8.3) μg/mL. The half-life was 2.3 (0.5) hours, and clearance averaged 0.20 (0.03) L/(h·kg). Comparing the capsule and liquid formulations using the geometric least-squares mean ratios of the 3 bioequivalence metrics ($C_{\text{max}}$, $AUC_{\text{last}}$, and $AUC_{\infty}$), the formulations were nearly 100% identical and well within the 90% confidence limits (Table 3).

Noncompartmental Analysis

Noncompartmental analyses were performed in children (≥2 to ≤5 years) in arm 1 and in the single participant in arm 2 who withdrew prior to completion of the second PK visit as well as in older children (>5 to ≤17 years) in arm 2. In young children, following a mean (SD) dose of 22.7 (3.0) mg/kg of HU, absorption was rapid with a mean (SD) $T_{\text{max}}$ of 0.57 (0.34) hours. The decline phase after a $C_{\text{max}}$ of 37.4 (9.3) μg/mL was well captured, and the average half-life was 1.96 (0.18) hours. The mean residence time (MRT) was small, averaging 2.6 (0.3) hours. The apparent clearance was consistent among these subjects, averaging 0.234 (0.028) L/(h·kg). In older children (arm 2), HU was rapidly absorbed with a $T_{\text{max}}$ of 0.86 (0.53) hours, mean $C_{\text{max}}$ was 33.8 (8.3) μg/mL, and the mean half-life was 2.31 (0.47) hours. The MRT was also small, averaging 2.8 (0.4) hours.
Comparison of Pharmacokinetic Studies

Table 4 provides a summary of existing studies assessing the PK properties of HU in patients with SCA. Children from the bioavailability analysis (arm 2) and those from the single-dose (arm 1) analysis are presented separately.

Population Pharmacokinetic Modeling

Individual HU concentration-time profiles are shown in Figure S1. The available data consisted of 682 plasma concentrations with 62 measurements (60 predose) below the level of quantification. Five predose concentrations were above the limit of quantification and were treated as outliers.

A 1-compartment model with first-order absorption was initially used to describe the data. However, delayed absorption in several children required a more flexible model. Therefore, a model with a series of transit compartments describing absorption and a 1-compartment model describing disposition were designed that successfully characterized the trend and variability in the data. Figure S2 demonstrates the goodness-of-fit plots of the final model. The individual and population predictions vs observed concentrations are symmetrically distributed around the line of identity. The visual predictive plots stratified by formulation are presented in Figure S3. Individual predicted concentration-vs-time profiles were very close to the experimental data (Figures S4a–d).

All PK parameters, intersubject, interoccasion, and residual error variances had CVs smaller than 55% (Table S3). The intraindividual variability for the number of transit compartments (N) tended to 0 during the model-building process and was fixed to 0. The intraindividual variability for MTT was not significantly different from 0 as tested by the decrease in the NONMEM objective function and was also fixed to 0. The IOV was tested only for MTT, as the absorption rate was the most likely reason for the PK difference seen for 2 consecutive visits of the participants.

The apparent volume of distribution equaled 45.4 L, and the apparent systemic clearance was 11.9 L/h for a theoretical patient of 70 kg. Allometric scaling accounted for the weight differences observed in disposition parameters (CL/F, V/F) with the standard exponent of 0.75 for clearance and 1 for distribution volume. The IIV for CL/F and V/F were small (CV % less than 10%). The mean absorption time was almost 2-fold greater for capsules (0.318 hours) than for liquid (0.181 hours), with high IOV of 63%. The graphical presentation of weight, sex, and formulation effects on PK parameters is provided in Figure 2.

Age, sex, height, and laboratory variables (Table 1) were not significant covariates in this study (data not shown).

Safety Results

All participants tolerated the single dose of hydroxyurea and all study-related procedures without apparent adverse events attributed to them. AE data are provided in Table S4.
Discussion

Hydroxyurea is a crucial therapy for children with SCA. Its off-label designation for children concerns parents and has been identified as a significant barrier to widespread acceptance. In addition, only having access to capsule formulations can impede pediatric use both because toddlers and many older children lack the ability to swallow capsules and because clinicians have difficulties in adapting fixed capsule formulations to dosing in small children. This trial specifically addresses pharmacologic limitations that had been identified by the FDA as necessary for regulatory approval for pediatric use and liquid formulation: comparative PK data on the bioavailability of liquid vs capsule formulations and the PK profile of HU in children across cohorts of different ages. Many drugs experience age-related differences in absorption, distribution, metabolism, and excretion that have therapeutic implications. Based on FDA guidelines, our data conclusively address both regulatory limitations. A liquid preparation of HU (100 mg/mL) diluted in cherry syrup is bioequivalent to Droxia® (200 mg) capsules. Furthermore, toddlers who received a liquid formulation of HU had similar PK profiles to older children who received either liquid or capsule formulations. Independent of formulation or age between 2 and 18 years, toddlers and children with SCA had rapid absorption that translated to a predictable disposition of the medication.

Currently, there are limited data evaluating the PK of HU in children. Previous studies have shown that HU has excellent oral bioavailability with rapid but variable absorption and rapid elimination with half-life of approximately 2 hours. In this prospective, open-label trial, we investigated the PK in children following ingestion of liquid and/or capsule formulations of HU followed by early and frequent blood sampling. Both formulations had rapid absorption (T_{max} 0.86 hours) with a peak concentration of 33.8 μg/mL. Interpersonal variation was observed in the absorption time of HU in both younger and older children. This variation has been reported and may be due to variations in transmembrane transporters. Between liquid and capsule formulations, the largest difference in the PK profiles was a trend toward a shorter time to peak concentration following ingestion of the liquid compared with the capsule, but that difference did not reach statistical significance (0.74 versus 0.97 hours, P = 0.14; Table 2). Pediatric PK data for HU are limited to 3 studies: observations from the internal pilot study (consisting of the first 22 participants) of the NIH-sponsored BABY HUG trial, a study of children with SCA administered an oral tablet formulation, and children receiving a first-dose of HU via a liquid suspension (Table 4). In the NIH-sponsored BABY HUG trial, as part of an internal pilot study, 22 very young children (mean age 14.7 months) underwent PK sampling following their first dose of liquid HU. PK samples were collected predose and then 1, 2, and 4 hours following ingestion. The C_{max} and AUC_{∞} (19.8 μg/mL and 68.8 μg · h/mL) were lower than our results and those of subsequently published pediatric studies. At the time, the authors felt this was suggestive that the PK profile of liquid HU in very young children may be different from that in adults. Subsequently, de Montalembert et al reported PK profiles in 11 children at a mean (SD) age of 10.2 (5.5) years who ingested a coated breakable HU tablet. The C_{max} in that population was 24.5 μg/mL, with an AUC_{∞} of 115.8 μg · h/mL. Finally, Ware et al performed PK testing following a first dose of HU (liquid, n = 77; capsule, n =
at mean (SD) age of 9.6 (4.8) years. Children given the liquid formulation had a lower peak concentration (25.4 μg/mL) and shorter half-life (1.64 hours) but a similar AUC∞ (91.9 μg · hr/mL) when compared with children given a capsule (31.9 μg/mL, 2.17 hours, and 101.0 μg · h/mL).

In contrast to previous studies in children, we pursued a protocol of early and aggressive monitoring of plasma concentrations. Liquid and capsule formulations resulted in similar AUC∞, similar Cmax, and similar half-life (Table 2). In our participants, 21.0% (8/39) of children receiving a liquid formulation reached a peak drug concentration between 30 and 60 minutes. The first scheduled blood sampling in the BABY HUG trial’s internal pilot occurred at 1 hour following HU ingestion. This time point was likely after the peak concentration had been reached and during the precipitous phase of drug elimination, which may have potentially overestimated the Tmax and underestimated the Cmax and AUC∞. All 11 children reported by de Montalembert et al reached Tmax at the first blood sample draw, which was 45 minutes following dosing. This timing also suggests that participants may have reached Tmax prior to sampling. In contrast, the 77 children reported by Ware et al included early blood sampling (15 and 30 minutes postdose). However, samples were not obtained between 30 minutes and 1 hour, which is the time frame that 1 in 5 children given the liquid reached peak drug concentrations in our cohort. That timing may have led to a longer calculated Tmax and underestimated Cmax and AUC∞.

We report that a population PK model was successfully developed to describe the time course of HU concentrations after oral administration in children with SCA. This model adequately captured the variability in absorption and disposition of HU. Body weight was found to influence both the apparent clearance and volume of distribution and was the main factor that varied with age. Measures of medication exposures (AUC- or CL/F-related) were not altered by formulation; therefore, dosing adjustments are not required for transitioning from one formulation to another. Additionally, this model offers confidence, with respect to dosing and PK, that current standard-practice dosing schemes that adjust for weight result in similar drug exposures over time.

One limitation of this study is that we did not ascertain if differences exist in PK parameters following a single dosage and during steady-state sampling with chronic daily administration. Although this was initially planned as an aim of this study, it was unable to be completed due to difficulty in recruiting participants. Also, this study did not assess the PK of HU in infants or in children less than 2 years of age.

In summary, a solution of HU in cherry syrup compared with Droxia® capsules meets FDA requirements of bioequivalence in children. Our results demonstrate that (1) exposure to HU is not significantly altered based on liquid or capsule formulation, making dosing adjustments for differences in either drug formulation or age unnecessary, and (2) standard weight-based dosing schemes of HU provide consistent drug exposure. These data support the use of liquid HU in children who are unable to swallow capsules and in those whose low weight precludes the use of fixed capsule formulations. These findings should encourage the use of HU across the spectrum of both age and weight in children with SCA, and they should facilitate the expanded use of HU as recently recommended in the NHLBI guidelines.
for care of children with SCA. Importantly, satisfying FDA regulatory requirements for pediatric approval of HU could address additional barriers to use.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

This clinical trial was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), under the authority of the Best Pharmaceuticals for Children Act (BPCA), contract no. HHSN201000003I/task order no. HHSN27500004 (K.A.N. and Z.R.).

The authors would like to thank the children and families who participated in the study. The authors also appreciate the efforts of the laboratory personnel, study coordinators, and nursing staff at each of the participating institutions.

**References**


The Pediatric Trials Network Administrative Core Committee

Daniel K. Benjamin Jr, Duke Clinical Research Institute, Durham, NC; Katherine Y. Berezny, Duke Clinical Research Institute, Durham, NC; Edmund Capparelli, University of California–San Diego, San Diego, CA; Michael Cohen-Wolkowiez, Duke Clinical Research Institute, Durham, NC; Gregory L. Kearns, Children’s Mercy Hospital, Kansas City, MO; Matthew Laughon, University of North Carolina at Chapel Hill, Chapel Hill, NC; Andre Muelenaer, Virginia Tech Carilion School of Medicine, Roanoke, VA; T. Michael O’Shea, Wake Forest Baptist Medical Center, Winston Salem, NC; Ian M. Paul, Penn State College of Medicine, Hershey, PA; P. Brian Smith, Duke Clinical Research Institute, Durham, NC; John van den Anker, George Washington University School of Medicine and Health, Washington, DC; Kelly Wade, Children’s Hospital of Philadelphia, Philadelphia, PA; Thomas J. Walsh, Weill Cornell Medical College of Cornell University, New York, NY.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development: David Siegel, Perdita Taylor-Zapata, Anne Zajicek, Alice Pagan.
The Emmes Corporation (Data Coordinating Center): Ravinder Anand, Gina Simone.
Figure 1.
Representative hydroxyurea concentration (μg/mL) per time (hour) profiles in 4 selected children who were given both liquid (–○–) and capsule (–●–) formulations.
Figure 2.
Relationship of body-weight-normalized apparent clearances (CL/F/BW and CL/F/BW^0.75) vs age for all children. Closed symbols (●) denote males, and open symbols (○) denote females.
Table 1
Demographic, Baseline Laboratory Parameters, and Hydroxyurea Dosage by Study Arm

<table>
<thead>
<tr>
<th>Category</th>
<th>Arm 1, n = 16</th>
<th>Arm 2, n = 23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2–3 Years</td>
<td>4–5 Years</td>
</tr>
<tr>
<td></td>
<td>n = 6</td>
<td>n = 10</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>3.1 (0.5)</td>
<td>4.8 (0.5)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>96.3 (4.8)</td>
<td>109.5 (5.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>14.8 (1.4)</td>
<td>18.2 (2.2)</td>
</tr>
<tr>
<td>Baseline laboratory parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, 10^3/L</td>
<td>11.9 (3.2)</td>
<td>10.6 (4.0)</td>
</tr>
<tr>
<td>Hb, g/L</td>
<td>87.7 (15.8)</td>
<td>86.9 (10.2)</td>
</tr>
<tr>
<td>MCV, fL</td>
<td>90.4 (8.6)</td>
<td>93.9 (12.5)</td>
</tr>
<tr>
<td>Platelets, 10^3/L</td>
<td>432 (172)</td>
<td>402 (167)</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140.0 (1.9)</td>
<td>138.0 (1.8)</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.5 (0.6)</td>
<td>4.3 (0.2)</td>
</tr>
<tr>
<td>BUN, mmol/L</td>
<td>2.6 (1.3)</td>
<td>3.1 (0.9)</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>23.8 (11.4)</td>
<td>28.6 (5.1)</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>178.7 (30.5)</td>
<td>153.3 (25.1)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>47.2 (11.8)</td>
<td>43.2 (13.4)</td>
</tr>
<tr>
<td>Bilir T, μmol/L</td>
<td>33.1 (12.7)</td>
<td>31.8 (14.4)</td>
</tr>
<tr>
<td>Hydroxyurea dose, mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid</td>
<td>23.6 (3.0)</td>
<td>24.1 (4.2)</td>
</tr>
<tr>
<td>Capsule</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; WBC, white blood cell; Hb, hemoglobin; MCV, mean corpuscular volume; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate aminotransferase; Bilir T, total bilirubin; N/A, not applicable.
### Table 2
Pharmacokinetic Parameters in Children in Arm 2 for Capsule and Liquid Formulations of Hydroxyurea

<table>
<thead>
<tr>
<th>Parameters, Mean (SD)</th>
<th>Both n = 44</th>
<th>Capsule n = 22</th>
<th>Liquid n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/mL)</td>
<td>33.8 (8.3)</td>
<td>33.6 (8.2)</td>
<td>34.0 (8.7)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hour)</td>
<td>0.86 (0.53)</td>
<td>0.97 (0.52)</td>
<td>0.74 (0.5)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;last&lt;/sub&gt; (μg · h/mL)</td>
<td>101.7 (24.7)</td>
<td>103.0 (25.4)</td>
<td>100.3 (24.6)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt; (μg · h/mL)</td>
<td>114.1 (29.4)</td>
<td>116.3 (30.0)</td>
<td>111.9 (29.4)</td>
</tr>
<tr>
<td>λ&lt;sub&gt;z&lt;/sub&gt; (hour)</td>
<td>0.31 (0.05)</td>
<td>0.31 (0.05)</td>
<td>0.31 (0.05)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hours)</td>
<td>2.3 (0.5)</td>
<td>2.3 (0.5)</td>
<td>2.3 (0.5)</td>
</tr>
<tr>
<td>MRT (hours)</td>
<td>2.8 (0.4)</td>
<td>2.9 (0.4)</td>
<td>2.8 (0.4)</td>
</tr>
<tr>
<td>CL/F/BW (L/[hr · kg])</td>
<td>0.20 (0.03)</td>
<td>0.20 (0.03)</td>
<td>0.21 (0.04)</td>
</tr>
</tbody>
</table>

C<sub>max</sub>: maximum observed plasma concentration; T<sub>max</sub>: time to maximum plasma concentration; AUC<sub>last</sub>: area under the concentration-vs-time curve calculated using the log-linear trapezoidal method from time 0 to the last quantifiable concentration; AUC<sub>∞</sub>: area under the concentration-vs-time curve calculated using the log-linear trapezoidal method from time 0 extrapolated to time ∞; λ<sub>z</sub>: terminal elimination slope constant; t<sub>1/2</sub>, terminal elimination half-life calculated as ln2/λ<sub>z</sub>; MRT: mean residence time; CL/F/BW, clearance normalized for body weight. Parameters for liquid and capsule formulations compared with a paired 2-tailed t-test, and none were significantly different.
### Table 3

Assessment of Hydroxyurea Bioavailability via FDA Guidelines

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Geometric LS Mean</th>
<th>90% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capsule</td>
<td>Liquid</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (μg/mL)</td>
<td>32.3</td>
<td>33.1</td>
</tr>
<tr>
<td>AUC_{last} (μg · h/mL)</td>
<td>100.3</td>
<td>98.6</td>
</tr>
<tr>
<td>AUC_{∞} (μg · h/mL)</td>
<td>113.3</td>
<td>110.1</td>
</tr>
</tbody>
</table>

Abbreviations defined in Table 2; LS indicates least-squares.
Summary of Published Pharmacokinetic Parameters of Hydroxyurea

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Age, Years</th>
<th>Dose, mg/kg</th>
<th>Formulation</th>
<th>$C_{max}$, μg/mL</th>
<th>AUC$_{0-\infty}$, μg · h/mL</th>
<th>$T_{max}$, hr</th>
<th>$t_{1/2}$, hr</th>
<th>CL/F/BW, L/(h · kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>–</td>
<td>17</td>
<td>4.5 (1.7)</td>
<td>22.7 (3.0)</td>
<td>liquid</td>
<td>37.4 (9.3)</td>
<td>104.5 (18.8)</td>
<td>0.57 (0.34)</td>
<td>1.96 (0.18)</td>
<td>0.234 (0.028)</td>
</tr>
<tr>
<td>Arm 2</td>
<td>–</td>
<td>22</td>
<td>12.0 (3.6)</td>
<td>21.7 (6.4)</td>
<td>liquid</td>
<td>34.0 (8.7)</td>
<td>111.9 (29.4)</td>
<td>0.74 (0.52)</td>
<td>2.3 (0.5)</td>
<td>0.205 (0.035)</td>
</tr>
<tr>
<td>Arm 2</td>
<td>–</td>
<td>22</td>
<td>12.0 (3.6)</td>
<td>22.6 (4.9)</td>
<td>capsule</td>
<td>33.6 (8.2)</td>
<td>116.3 (30.0)</td>
<td>0.97 (0.52)</td>
<td>2.31 (0.47)</td>
<td>0.20 (0.03)</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rogers et al$^{16}$</td>
<td>2005</td>
<td>22</td>
<td>1.2 (NR)</td>
<td>20</td>
<td>liquid</td>
<td>19.8 (5.8)</td>
<td>68.8 (11.5)</td>
<td>NR</td>
<td>2.36 (0.99)</td>
<td>NR</td>
</tr>
<tr>
<td>Ware et al$^{17}$</td>
<td>2011</td>
<td>87</td>
<td>9.6 (4.8)</td>
<td>20</td>
<td>liquid</td>
<td>26.1 (6.8)</td>
<td>93.0 (23.4)</td>
<td>0.82 (0.47)</td>
<td>1.70 (0.53)</td>
<td>0.24 (0.09)</td>
</tr>
<tr>
<td>de Montalembert et al$^{18}$</td>
<td>2006</td>
<td>11</td>
<td>10.2 (5.5)</td>
<td>21.9</td>
<td>tablets</td>
<td>24.5</td>
<td>115.8</td>
<td>0.75</td>
<td>6.3</td>
<td>0.127</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Montalembert et al$^{18}$</td>
<td>2006</td>
<td>15</td>
<td>30.1</td>
<td>20.9</td>
<td>both</td>
<td>26.5</td>
<td>128.4</td>
<td>0.86</td>
<td>6.3</td>
<td>0.154</td>
</tr>
<tr>
<td>Yan et al$^{19}$</td>
<td>2005</td>
<td>7</td>
<td>~40</td>
<td>15</td>
<td>capsule</td>
<td>28.3 (11.0)</td>
<td>82.5 (15.5)</td>
<td>0.5</td>
<td>3.14</td>
<td>0.194</td>
</tr>
</tbody>
</table>

Abbreviations are defined in Table 2; NR indicates not reported. Data presented are mean (standard deviation).