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Model Informed Dose Optimization of Dichloroacetate for the Treatment of Congenital Lactic Acidosis in Children

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Abstract

Dichloroacetate (DCA) is an investigational drug used to treat congenital lactic acidosis and other mitochondrial disorders. Response to DCA therapy in young children may be suboptimal following body weight–based dosing. This is because of autoinhibition of its metabolism, age-dependent changes in pharmacokinetics, and polymorphisms in glutathione transferase zeta 1 (GSTZ1), its primary metabolizing enzyme. Our objective was to predict optimal DCA doses for the treatment of congenital lactic acidosis in children. Accordingly, a semimechanistic pharmacokinetic-enzyme turnover model was developed in a step-wise approach: (1) a population pharmacokinetic model for adults was developed; (2) the adult model was scaled to children using allometry and physiology-based scaling; and (3) the scaled model was externally qualified, updated with clinical data, and optimal doses were projected. A 2-compartment model accounting for saturable clearance and GSTZ1 enzyme turnover successfully characterized the DCA PK in adults and children. DCA-induced inactivation of GSTZ1 resulted in phenoconversion of all subjects into slow metabolizers after repeated dosing. However, rate and extent of inactivation was 2-fold higher in subjects without the wild-type EGT allelic variant of GSTZ1, resulting in further phenoconversion into ultraslow metabolizers after repeated DCA administration. Furthermore, DCA-induced GSTZ1 inactivation rate and extent was found to be 25-to 30-fold lower in children than in adults, potentially accounting for the observed age-dependent changes in PK. Finally, a 12.5 and 10.6 mg/kg twice-daily DCA dose was optimal in achieving the target steady-state trough concentrations (5–25 mg/L) for EGT carrier and EGT noncarrier children, respectively.

Keywords

dichloroacetate; congenital lactic acidosis; pediatrics; dose optimization; phenoconversion

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

Congenital lactic acidosis (CLA) is a rare genetic disorder that consists of a group of inborn errors of mitochondrial metabolism, characterized by abnormal accumulation of lactate in body fluids and tissues. CLA is primarily caused by mutations in nuclear or mitochondrial DNA that encode genes of the pyruvate dehydrogenase complex (PDC) or enzymes in the respiratory chain.¹ Signs of disease often occur very early in life and include lactic acidosis and progressive neurological and neuromuscular degeneration.² Currently, there are no Food and Drug Administration–approved therapies for these life-threatening diseases.

Dichloroacetate (DCA) is an investigational drug effective in reducing blood and cerebrospinal fluid lactate concentrations in patients with CLA, including PDC deficiency. The PDC megacomplex is a gatekeeper enzyme linking cytoplasmic glycolysis with the mitochondrial tricarboxylic acid cycle and oxidative phosphorylation. PDC undergoes reversible phosphorylation in humans by pyruvate dehydrogenase kinase (PDK), which inhibits the enzyme, and pyruvate dehydrogenase phosphatase, which restores PDC catalytic activity.^{3–5} DCA activates PDC by directly inhibiting PDK and by decreasing PDC enzyme turnover, thereby facilitating oxidative removal of lactate.^{6,7}

Despite its efficacy, optimal dosing of DCA has been challenging in both adults and children because both populations are treated according to a fixed weight-based dosing regimen.^{8,9} The major limitation of this approach is that it does not consider the effects of well-known pharmacological variables that can influence DCA's kinetics and biotransformation. For example, it has been shown that the half-life of DCA increases after repeated administration in adults and children. This phenomenon is attributable to the drug's mechanism-based inhibition of glutathione transferase zeta 1 (*GSTZ1*), which dechlorinates DCA to glyoxylate.¹⁰ This autoinhibition of DCA's biotransformation pathway makes it difficult to predict changes in plasma drug clearance and consequently dose during treatment. Moreover, plasma half-life increased approximately 10-fold after 6 months of daily administration in adults, whereas half-life increased only about 2.5-fold in children, suggesting that age-dependent changes may play a role in the metabolism of DCA.¹⁰ Finally, it is known that *GSTZ1* is polymorphic,^{11,12} resulting in the expression of 5 major haplotypes: EGT (wild type, 45%–55% of the population), KGT (25%–35% of the population), EGM (10%–20% of the population), KRT (1%–10% of the population), and KGM (<1% of the population).¹³ Subjects who have at least 1 EGT allele (EGT carriers) clear the drug from plasma faster than those who do not possess EGT allele(s)^{14,15} (EGT noncarriers).

In light of these challenges, the objective of this study was to develop a population pharmacokinetic (PopPK) model for DCA to predict optimal DCA dosing regimens in children. This was achieved in a stepwise manner: (1) a PopPK model for DCA in healthy adults was developed; (2) the developed model was then scaled to children, using data from a randomized, controlled trial of DCA in children with CLA; and (3) the scaled model was further refined and updated, and optimal doses for children are recommended.

Materials and Methods

Data for Model Development

Data for building the model were collected from prior studies of DCA in adults¹⁴ and children⁹ that investigated the effect of single and repeated doses on its pharmacokinetics and the influence of GSTZ1 polymorphisms. All studies were conducted in the Clinical Research Center of Shands Hospital at the University of Florida after approval by the university's institutional review board. Informed consent was obtained from all participants or parents/guardians prior to subject enrollment.

Adult Data—The demographic characteristics of the adult population¹⁴ are presented in Table 1. Briefly, 12 participants (5 males), aged 26 ± 4.5 years were genotyped for *GSTZ1* haplotype status and were administered an oral dose of 25 mg/kg/day DCA for 5 consecutive days. The 1,2-¹³C-DCA was administered on day 1 and day 5, whereas 1,2-¹²C-DCA was administered on days 2–4. Plasma kinetics were investigated on days 1 and 5, and DCA concentrations were measured by gas chromatography–mass spectrometry.

Seven subjects possessed the EGT allelic variant of *GSTZ1* (EGT carriers), and 5 of them lacked this variant (EGT noncarriers). Four EGT carriers were homozygous, whereas 3 were heterozygous (1-EGT/KGT, 2-EGT/KRT). Subject 12 was excluded from the analysis as the subject possessed an extremely rare nonsynonymous¹⁴ single-nucleotide polymorphism in addition to a rare KGM allelic variant of *GSTZ1*.

Data in Children—The demographic characteristics of the pediatric population⁹ are presented in Table 1. Forty-three children with CLA, aged 0.9–19 years at entry, were enrolled. All patients were genotyped for *GSTZ1* haplotype status and received placebo for 6 months. Thereafter, patients were randomized to receive either placebo ($n = 22$) or DCA ($n = 21$) for an additional 6 months. After this initial 12-month period, all patients were treated with open-label DCA for a minimum of 12 additional months. DCA kinetics were evaluated following administration of 12.5 mg/kg of 1,2-¹³C-DCA on day 1 and thereafter every 6 months for up to 60 months. During these 6-month intervals, patients were administered 12.5 mg/kg of 1,2-¹²C-DCA every 12 hours. Of the 21 patients in the original DCA group, 5 patients did not complete the study because of disease-related death (3) or dropout (2). Hence, data from 16 children (11 EGT carriers and 5 EGT noncarriers), aged 5.9 ± 4.9 years at entry, were included and analyzed via a nonlinear mixed-effects modeling approach.

Modeling and Simulation

A stepwise approach for modeling and simulation was adopted (Figure 1). First, an in vitro–in vivo correlation (IVIVC) of GSTZ1 enzyme kinetic data was performed. Using these IVIVC values, clinical data and GSTZ1 enzyme turnover,¹⁶ a PopPK model for adults was developed. Second, the adult PopPK model was scaled to the children, and the model predictions were externally qualified with the observed DCA concentrations measured in children and model parameterization was further updated if needed. Finally, clinical trial simulations were run to predict optimal doses for children.

Development of Adult PopPK Model

Structural Model—A PopPK model was developed in NONMEM v.7.3 (Icon Development Solutions, Dublin, Ireland) using plasma concentration–time data obtained from healthy adult volunteers.¹⁴ One-compartment and 2-compartment models were explored as structural models. Nonlinear biotransformation of DCA by the GSTZ1 enzyme¹⁷ was characterized by considering Michaelis-Menten¹⁸ kinetics using maximal velocity ($V_{\max}$) and Michaelis constant (K_m) parameters. Adult human in vitro estimates for $V_{\max}$ and K_m were obtained from the literature¹⁹ and scaled to corresponding in vivo values by accounting for GSTZ1 protein expression and the estimated liver weight of adults according to equations 1 and 2.

$$V_{\max, \text{ in vivo}} = V_{\max, \text{ in vitro}} * \text{CPPGL} * \text{Liver weight} \quad (1)$$

$$K_{m, \text{ in vivo}} = K_{m, \text{ in vitro}} \quad (2)$$

where CPPGL (cytosolic protein per gram of liver) is 71 mg/g of liver²⁰ and liver weight is 1500 g for an average 70-kg adult.

After performing IVIVC, the calculated in vivo values for $V_{\max}$ and K_m were 4.6 mg/h/kg and 6.1 mg/L, respectively, which were fixed in the model. The turnover rate of free GSTZ1 enzyme was considered by accounting for natural synthesis (K_{syn}), a zero-order rate constant, and degradation of the enzyme (K_{deg}), a first-order rate constant. Literature evidence¹⁶ suggests that it takes approximately 2 months for GSTZ1 to recover to its baseline activity after inhibition by a single oral dose of DCA. This phenomenon corresponds to an estimated half-life of 0.0026 1/h (K_{deg}), which was fixed in the model. DCA-induced autoinhibition of GSTZ1 was incorporated into the model using a function that characterizes the change in $V_{\max}$ by a first-order inactivation constant (K_{inac}). Mathematically, this translates into the following set of differential equations (Figure 2):

$$\frac{dV_{\max}}{dt} = K_{\text{syn}} - K_{\text{deg}} * V_{\max} - K_{\text{inac}} * \frac{V_{\max} * C}{K_m + C} \quad (3)$$

With

$$V_{\max(0)} = V_{\max0};$$

$V_{\max0}$ = Starting maximal velocity of GSTZ1 mediated metabolism

$$V_{\max(t)} = V_{\max0} + \int_0^t \frac{dV_{\max}}{dt} \quad (4)$$

In this model, we are assuming that the system is at steady state at baseline in the absence of DCA. However, when DCA is administered, a metabolite intermediate covalently binds to free GSTZ1, forming a complex that undergoes further transformation to ultimately release an inactive enzyme. This inhibitory effect is considered concentration dependent, with a greater extent of inhibition of GSTZ1 expected at higher concentrations of DCA. Consequently, the enzymatic activity of the GSTZ1 enzyme decreases in a nonlinear fashion (equation 3). The residual activity at any time ($V_{\max(t)}$) will depend on the duration of DCA exposure (t) and the starting GSTZ1 activity present in the population ($V_{\max 0}$) under study (equation 4).

Variance Model—Between-subject variability (BSV) was assumed to be log-normally distributed, with a mean of zero and a variance of σ^2 . Models using additive error, multiplicative error, and a combination of both additive and multiplicative errors were tested to account for residual variability. Once a base model was identified, we tested the effect of covariates such as *GSTZ1* genotype on different model parameters by employing physiological plausibility and statistical criteria (forward inclusion, OFV of 3.83; backward exclusion, OFV of 6.63). The robustness and reliability of the final model were tested based on goodness-of-fit plots (eg, observations vs population predictions, observations vs individual predictions, conditional weighted residuals vs population predictions, and conditional weighted residuals vs time after last dose) and physiological meaningfulness of parameters (eg, comparison of model-estimated parameters with other clinical studies or known information about DCA).

Development of PopPK Model in Children

The adult PopPK model was scaled to children using enzyme expression and activity levels²⁰ of GSTZ1 to scale enzymatic capacity ($V_{\max 0}$) and body weight-based scaling for central volume of distribution (V_1). Other parameters, such as K_A , K_{deg} , and K_{inac} , were assumed to be the same in adults and children because studies to demonstrate otherwise have not been performed. These assumptions were tested quantitatively by performing model-based predictions of concentrations (median and 95% prediction intervals) in children that were overlaid with observed concentrations⁹ in children. Finally, the developed PopPK model was further updated using the observed clinical data in children.

For the variance model, BSV was assumed to be log-normally distributed to identify random-effects parameters. For residual variability, a combined error model was used with both additive and proportional error components in it. The final model was identified based on goodness-of-fit plots, residual plots, and the physiological meaningfulness of parameter estimates.

Simulations for Dose Projection

Using the developed PopPK model for children, clinical trial simulations were performed and steady-state trough levels were determined for EGT carrier and EGT noncarrier children of different weights (10–60 kg). Optimal doses were then selected based on matching of steady-state trough concentrations with the known therapeutic range of DCA (5–25 mg/L) in children.²¹

Results

Adult Data

Noncompartmental analysis obtained from this study¹⁴ revealed that the plasma half-life of DCA after the first dose was similar in adult EGT carriers and EGT noncarriers on day 1 (1.1 ± 0.5 vs 1.2 ± 0.5 hours). However, the DCA half-life on day 5 was 4.5-fold lower in EGT carriers than in EGT noncarriers (3.9 ± 1.4 vs 18.1 ± 12.1 hours). These findings indicate that the half-life of DCA changes after repeated administration and that the magnitude of that change may be dependent on *GSTZ1* haplotype.

Data in Children

Noncompartmental analysis of the data revealed that the half-life of DCA was higher after 6 months of exposure in both EGT carriers (5.2 ± 4.6 hours) and EGT noncarriers (15.9 ± 13.1 hours), compared with the DCA-naïve subjects (1.4 ± 0.4 hours). After 6 months of exposure, the half-life of DCA did not change substantially until 30 months of DCA exposure in both EGT carriers and EGT noncarriers. However, in EGT carriers, there was an interesting trend of reduced plasma half-life 36 months onward. Interestingly, it was found that the data beyond 30 months of exposure were only available in a set of twins who seemed to have faster clearance compared with the rest of the EGT carriers.

Development of Adult PopPK Model

A 2-compartment body model (Figure 2) with nonlinear clearance from the central compartment ($V_{\max}$, K_m) was able to characterize the DCA PK in adults after its administration on day 1 and day 5 (Supplementary Figure S1). However, there were slight underpredictions, mainly in the absorption phase, which can be attributed to high variability in the data. The autoinhibitory effect of DCA on its metabolism explained the observed increase in half-life on day 5, compared with day 1, for both EGT and EGT noncarriers. *GSTZ1* genotype had a covariate effect on the clearance of DCA, because EGT noncarriers had an approximately 2-fold higher DCA-induced rate of enzyme inactivation (0.0715 1/h) compared with EGT carriers (0.0347 1/h); see Table 2. The total volume of distribution of DCA ($V_1 + V_2$) was estimated to be 0.535 L/kg, which corresponds to a volume of distribution of 37.4 L in an average 70-kg adult. These data suggest that the drug was able to distribute completely in extracellular fluids along with some intracellular fluids in the body. The rate of absorption of DCA was estimated to be 0.83 1/h, which is in agreement with other clinical studies.²²

For the random-effects model, BSV was significant for $V_{\max0}$ (24.1%), absorption rate constant (52%), V_1 (25.4%), and DCA-induced inactivation rate (20.2%). High BSV on K_A was consistent with the high variability of the data, particularly in the absorption phase. A combined error model (multiplicative + additive) was found appropriate to characterize the residual variability.

Development of a PopPK Model in Children

The developed adult PopPK model was successfully scaled and externally qualified in the pediatric population. There was good agreement between the model predictions and

observations following a single dose of 1,2-¹³C-DCA administered after 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months of 1,2-¹²C-DCA exposure in EGT carrier children (Figure 3A). However, the overlay between clinical observations and predictions in the terminal phase (clearance) was not as good beyond 30 months of exposure, because of an apparent trend for an increase in plasma clearance 36 months onward (Figure 3A). Similarly, the model was able to predict the pharmacokinetics following a single dose of 1,2-¹³C-DCA administered after 6, 12, 18, 24, and 30 months of 1,2-¹²C-DCA exposure in EGT noncarrier children (Figure 3B). However, the model predicted much lower concentrations in the absorption phase, which was particularly evident in EGT noncarriers.

The PopPK model developed on the basis of adult data was successfully fitted to the data in children (Supplementary Figure S2), and model parameterization was updated (Table 2). Overall, the model captured the pediatric data well, with slight underpredictions in the absorption phase in some subjects. No trend was observed in conditional weighted residuals (CWRES)-versus-population predictions (PRED) and CWRES-versus-time after last dose (TALD) plots, indicating the suitability of the model (Supplementary figure S2). The model-estimated parameter values for starting metabolic capacity, that is, $V_{\max 0}$, total volume of distribution ($V_1 + V_2$), and K_A were 1.95 mg/h/kg, 0.66 L/kg, and 2.02 1/h, respectively. Furthermore, the DCA-induced inactivation rate, that is, K_{inac} , was estimated to be approximately 2-fold higher in EGT noncarrier (0.0024 1/h) than EGT carrier (0.0013 1/h) children.

For the random-effects model, BSV was found to be relatively high for the parameters, mainly for V_2 and CL_D . Similar to what was demonstrated in adults, a combined error model (multiplicative + additive) was appropriate in children to characterize the residual variability.

Simulations for Dose Projection

Dose projections for EGT carrier and EGT noncarrier children are presented in Table 3. Clinical trial simulations revealed that the clearance of DCA becomes highly nonlinear at doses $> \sim 12.5$ mg/kg in EGT carriers and $> \sim 10.6$ mg/kg in EGT noncarriers (Supplementary Figure S3). In addition, a 12.5 mg/kg twice-daily dose was sufficient to achieve target steady-state trough concentrations (5–25 mg/L) in EGT carrier children. However, a 12.5 mg/kg dose would result in supratherapeutic trough concentrations ranging from 44 to 179 mg/L in EGT noncarrier children, potentially resulting in toxicity issues with chronic exposure. Furthermore, we found that a 15% reduction in dose to 10.6 mg/kg twice daily would be optimal to achieve target steady-state trough concentrations (5–25 mg/L) in EGT noncarrier children. The steady-state concentrations were found to decrease nonlinearly with the increasing body weight of children for both EGT carrier and EGT noncarrier children. However, this did not affect the optimal dose because the trough concentrations were still within the predefined therapeutic range (5–25 mg/L).

Discussion

In traditional drug development, doses for children are usually determined by extrapolating from adult data, if it is reasonable to assume that the disease progression, response to the

intervention, and exposure–response relationship are similar in children and adults.^{23,24} In such a case, a sponsor is usually required to conduct only a PK study to select a dose to achieve similar exposure (full extrapolation) or similar target PD effect (partial extrapolation) as attained in adults.^{23,24} For DCA, studies have shown that steady-state trough concentrations of 5–25 mg/L are correlated with the clinical efficacy of DCA in adults²⁵ as well in children.²¹ Consequently, a full extrapolation approach coupled with existing exposure–response information in children was used to inform dosing in children. This approach also allowed us to better understand the determinants of DCA plasma clearance, separate system-specific from drug-specific parameters, and explore the potential reasons for the age-dependent kinetics observed in earlier studies.

In the adult PK study,¹⁴ it was shown that the EGT carriers and noncarriers had similar half-lives after the first dose, whereas the magnitude of the increase in half-life after repeated dosing was smaller in EGT carriers (3.5-fold) than in EGT noncarriers (15-fold). This observation indicated that the clearance of DCA is a composite phenomenon, governed by 3 main factors: (1) the turnover rate of GSTZ1, (2) the initial GSTZ1 enzymatic capacity of the population, and (3) the DCA-induced inactivation rate of the protein.²⁶ We assumed the turnover rate of GSTZ1 enzyme to be the same for both EGT carrier and EGT noncarrier adults, although this assumption has not been tested experimentally. The base model accounting for natural enzyme turnover and the DCA-induced inactivation of GSTZ1 were able to explain the similar half-life estimates for EGT carriers and EGT noncarriers on day 1. However, it failed to capture the observed differential increase in half-life because of autoinhibition for EGT noncarriers (15-fold) and EGT carriers (3.5-fold) after 5 days of drug administration. Various possibilities were investigated to account for this interesting finding. One study²⁰ showed that the expression and in vitro enzymatic activity of GSTZ1 is similar between different GSTZ1 diplotypes. Moreover, if the enzymatic capacity differed between the 2 groups, the effect of having a lower capacity should have resulted in lower clearance (higher half-life) estimates in EGT noncarriers after the first dose, which was not observed. The effect of DCA on GSTZ1 activity was manifested only after repeated drug administration, ruling out the possibility of different enzymatic capacity. The most likely scenario to explain this dissimilarity is that the interaction of GSTZ1 and DCA may differ between EGT carriers and noncarriers. Our results suggest that EGT noncarriers have a higher rate and extent of GSTZ1 enzyme inactivation by DCA, resulting in greater autoinhibition and slower plasma clearance in EGT noncarriers. Because the autoinhibition phenomenon is more likely to occur after repeated dosing, this would also explain the finding that there was no difference in half-life between EGT carriers and noncarriers after the first dose of DCA. This postulate is consistent with an in vitro study²⁷ that demonstrated that the magnitude of DCA-induced inactivation effect of *GSTZ1* is system specific and differs between different *GSTZ1* haplotypes. Based on these findings, we hypothesize that autoinhibition phenoconverts both EGT carriers and noncarriers into slow metabolizers after repeated DCA administration, a phenomenon known as “phenoconversion,” reported for many drugs^{28–31} that are predominantly metabolized by phase I enzymes. However, the magnitude of phenoconversion is higher for EGT noncarriers, which converts them into ultraslow metabolizers compared with EGT carriers. Accordingly, a covariate effect of the

GSTZ1 genotype on K_{inac} was able to explain the differential increase in half-life seen on day 5 of drug exposure between adult EGT carriers and EGT noncarriers.

Once developed, the PopPK model was successfully extrapolated to children using allometry and physiologically based scaling of model parameters. That there were no significant differences in half-life¹⁰ between adults (2.1 ± 1.5 hours) and children (2.5 ± 0.4 hours) after a single DCA administration indicated that the clearance of DCA is similar between these groups. This assumption is supported by an in vitro study²⁰ that showed that the age-related differences in *GSTZ1* enzyme expression and activity disappeared when activity was adjusted for expression by accounting for the higher mass ratio of liver to body weight in children.³² Hence, the body weight-based scaling of V_{max0} was justified in our model. In EGT carrier children, our model slightly underpredicted clearance, especially beyond 36 months of exposure. This was because data beyond 36 months of exposure were only available for a set of twins, who seemed to show faster clearance compared with other EGT carriers. This could be an artifact, mainly because of smaller sample size ($n = 2$) after 36 months of exposure. It is also possible that, in addition to *GSTZ1* genetics, there may be other, yet unknown factors that can play significant roles in determining the clearance of DCA. There was also a slight mismatch between clinical observations and predictions in the absorption phase that was particularly evident in EGT noncarrier children, suggesting that the rate of absorption and/or rate of elimination may be different between adults and children. This hypothesis is supported by a much higher estimate of K_A in children compared with adults. Furthermore, the rates of DCA-induced *GSTZ1* enzyme inhibition for EGT carrier and EGT noncarrier children were estimated to be 25- to 30-fold lower compared with the adults, indicating that the autoinhibitory effect of DCA on *GSTZ1* is much slower in children compared with adults. This finding may explain the age dependence of DCA pharmacokinetics in children. In fact, studies^{27,33} have shown that the physiological concentrations of chloride anions inhibit DCA-induced *GSTZ1* inactivation, and this inhibitory effect is lower in adults compared with children. In other words, the reduced chloride-mediated inhibitory effect in adults is reflected in a higher rate and extent of *GSTZ1* inactivation and hence more change in clearance after chronic DCA exposure compared with what occurs in children. However, similar to the finding in adults, the magnitude of DCA-induced inactivation was estimated to be 2-fold higher in EGT noncarrier children than in EGT carrier children, which directly affects the clearance of DCA. This result suggests that dose adjustment may be needed in children, based on the presence of the EGT allele. Abdelmalak et al²¹ showed that steady-state DCA trough concentrations ranging from 5 to 25 mg/L were associated with clinical efficacy, that is, blood lactate-lowering in children. However, concentrations above 50 mg/L were found to be associated with toxicity, as exhibited primarily as an asymptomatic, reversible peripheral neuropathy. Based on this targeted trough range, a 12.5 mg/kg twice-daily dose was found optimal for EGT carrier children, whereas a 15% reduced dose, that is, a 10.6 mg/kg twice-daily dose was optimal for EGT noncarrier children. Although the trough concentrations were found to decrease nonlinearly with increasing weight of children, it did not affect the respective optimal DCA doses for EGT carrier and EGT noncarrier children.

We acknowledge certain limitations to this study. Although we were able to mechanistically quantify the differences in clearance between EGT carriers and EGT noncarriers, there still

exists a large, unexplainable variability among EGT carrier and EGT noncarrier children. The availability of subjects with rare diseases who may be available for pharmacokinetic-pharmacodynamic assessment is limited; hence, it becomes challenging to evaluate the impact of all potential covariates in such populations. For example, in the set of twins we studied, we could not exclude the possibility that their DCA PK may have been influenced by unknown factors, in addition to GSTZ1 polymorphisms. Another limitation of this study was that the doses for children were projected on the basis of limited information²¹ regarding the therapeutic range of plasma trough DCA levels (5–25 mg/L). Additional clinical studies are needed to confirm this range and/or better evaluate exposure–response relationship of DCA in children.

Conclusions

In summary, our mechanistic approach integrated information on DCA-induced GSTZ1 autoinhibition, GSTZ1 enzyme turnover, and the effect of GSTZ1 polymorphisms into a mathematical relationship that accurately predicts PK in children following chronic exposure to DCA. The model also indicated that the observed phenotypic differences in clearance between EGT carriers and noncarriers after repeated dosing are attributable to *GSTZ1* genotype–based phenoconversion. Moreover, children were found to exhibit a slower rate and extent of DCA-induced inactivation compared with adults, which may explain the observed differences in clearance after repeated dosing between these populations. Based on clinical trial simulations, we propose that a 12.5 and 10.6 mg/kg twice-daily dose of DCA would be optimal for EGT carrier and EGT noncarrier children, respectively. Following these DCA doses, trough concentrations should be measured to ensure exposure within the targeted therapeutic range. These recommendations may be further optimized when pharmacodynamic information becomes available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Stepwise workflow of the modeling and simulation approach.

Figure 2.

Schematic representation of the semimechanistic pharmacokinetic-enzyme turnover model for dichloroacetate (DCA). K_{syn} , natural synthesis rate of GSTZ1 enzyme; K_{deg} , natural degradation rate of GSTZ1 enzyme; K_{inac} (EGT carriers), DCA-induced GSTZ1-inactivation rate constant for EGT carriers; K_{inac} (EGT noncarriers), DCA-induced GSTZ1-inactivation rate constant for EGT noncarriers; K_A , first-order absorption rate constant; CL_D , intercompartmental clearance of DCA; V_{max} , maximum velocity of metabolism; K_m , affinity rate constant; V_1 , volume of distribution of plasma compartment; V_2 , volume of distribution of tissue compartment. DCA covalently binds to free GSTZ1 enzyme to form DCA-GSTZ1 complex, which releases degraded GSTZ1 enzyme, resulting in autoinhibition of DCA metabolism, represented by dashed red line.

Figure 3.

External model qualification in (A) EGT carrier children and (B) EGT noncarrier children using the developed PopPK model and scaled-up child parameters following a single oral dose of 1,2-¹³C-DCA after 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months of 1,2-¹²C-DCA exposure. Solid black diamonds represent observed mean DCA concentrations for all EGT carriers (including twins) along with standard deviation, solid red diamonds represent mean DCA concentrations for twins, black line represents predicted median concentration, gray bands represent 90% prediction interval, and n is the number of children from which the data were available (including twins).

Table 1Demographic Characteristics of the Adult¹⁴ and Pediatric Population⁹

Subject	Age at Entry (Years)	Sex	Population	GSTZ1 Genotype
EGT carrier adults				
1	24	F	Healthy	EGT/EGT
2	25	F	Healthy	EGT/EGT
3	24	M	Healthy	EGT/EGT
4	23	M	Healthy	EGT/EGT
5	26	F	Healthy	EGT/KGT
6	23	F	Healthy	EGT/KRT
7	25	F	Healthy	EGT/KRT
EGT noncarrier adults				
8	25	F	Healthy	KRT/KGT
9	37	M	Healthy	KGT/KGT
10	33	F	Healthy	KRT/KRT
11	21	M	Healthy	KRT/EGM
12 ^a	26	M	Healthy	KGM/KGT
EGT carrier children				
1	3.7	F	PDHE1	(EGT/EGT)
2	3.7	F	PDHE1	(EGT/EGT)
3	6	M	MELAS	(EGT/EGT)
4	9.6	F	Complex I	(EGT/KGT)
5	1.5	M	Complex II	(EGT/KGT)
6	1.7	F	PDHE1	(EGT/KGT)
7	4.8	M	PDHE1	(EGT/KGT)
8	9.7	M	COX	(EGT/KGT)
9	13.1	M	MELAS	(EGT/KGT)
10	19.1	F	MELAS	(EGT/KGT)
11	1.8	F	Complex I	(EGT/KRT)
EGT noncarrier children				
12	2.7	M	PDHE1	(KGT/KGM)
13	1.2	M	OXPHOS	(EGM/EGM)
14	7.1	M	Complex I and IV	(KGT/KGT)
15	2.3	M	Complex II, III, IV	(KGT/EGM)
16	5.8	F	PDHE1	(KGT/KGT)

MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; complex I, II, III, IV, deficiencies in the respective complexes in the respiratory chain; OXPHOS, generalized reduction in respiratory chain enzyme activities; PDHE1, deficiency in E1 alpha subunit of pyruvate dehydrogenase (PDH) component of PDC; COX, deficiency of cytochrome C oxidase.

^a This individual had a rare nonsynonymous single-nucleotide polymorphism in addition to rare KGM allele, excluded from the analysis.

Table 2
PopPK Model Fitted Parameters in Adults Along With Scaled and Fitted Parameters in Children

Parameters	Fitted Adult Parameters	Fitted Adult Parameters % BSV	Scaled Child Parameters	Fitted Child Parameters	Fitted Child Parameters % BSV
$V_{\max 0}$	322 mg/h fix ¹⁹	24.1	4.04 mg/h/kg	1.95 mg/h/kg	
K_m	6 mg/L Fix ¹⁹		6 mg/L	6 mg/L Fix ¹⁹	
K_{deg}	0.0026 1/h fix ¹⁶		0.0026 1/h	0.0026 1/h fix ¹⁶	
V_1	0.24 L/kg	25.4	0.24 L/kg	0.27 L/kg	25.7
V_2	0.29 L/kg		0.29 L/kg	0.39 L/kg	122.5
CL_D	3.78 L/h		3.78 L/h	0.91 L/h	143.2
K_A	0.83 1/h	52	0.83 1/h	2.02 1/h	46.4
$K_{\text{mac}}(\text{EGT carriers})$	0.0347 1/h	20.2	0.0347 1/h	0.0013 1/h	69.4
$K_{\text{mac}}(\text{EGT noncarriers})$	0.0715 1/h		0.0715 1/h	0.0024 1/h	
Residual variability estimates					
Proportional error	15.7 %		15.7 %	7.5 %	
Additive error	0.27 mg/L		0.27 mg/L	0.63 mg/L	

Table 3
Model Informed Dosing Regimen of DCA for EGT Carrier and EGT Noncarrier Children

Recommended Twice-Daily DCA Dose (mg/kg)	
EGT Carrier	EGT Noncarrier
12.5	10.6