HHS Public Access

Author manuscript

Pediatr Res. Author manuscript; available in PMC 2021 March 12.

Published in final edited form as:

Pediatr Res. 2020 December ; 88(6): 871–877. doi:10.1038/s41390-020-01140-8.

Theophylline Dosing and Pharmacokinetics for Renal Protection in Neonates with Hypoxic Ischemic Encephalopathy Undergoing Therapeutic Hypothermia

Adam Frymoyer[1], **Krisa P. Van Meurs**[1], **David R. Drover**[2], **Jelena Klawitter**[3], **Uwe Christians**[3], **Valerie Y. Chock**[1]

[1]Department of Pediatrics, Neonatal and Developmental Medicine, Stanford University School of Medicine, Stanford, CA;

[2]Department Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA;

[3]Department of Anesthesiology, University of Colorado, Aurora, CO.

Abstract

Background: Theophylline, a non-selective adenosine receptor antagonist, improves renal perfusion in the setting of hypoxia-ischemia and may offer therapeutic benefit in neonates with hypoxic ischemic encephalopathy (HIE) undergoing hypothermia. We evaluated the pharmacokinetics and dose-exposure relationships of theophylline in this population to guide dosing strategies.

Methods: A population pharmacokinetic analysis was performed in 22 neonates with HIE undergoing hypothermia who were part of a prospective study or retrospective chart review. Aminophylline (intravenous salt-form of theophylline) was given per institutional standard of care for low urine output and/or rising serum creatinine (5 mg/kg IV load then 1.8 mg/kg IV q6h). The ability of different dosing regimens to achieve target concentrations (4–10 mg/L) associated with clinical response was examined.

Correspondence: Adam Frymoyer, 750 Welch Rd, Suite #315, Palo Alto, CA 94304, frymoyer@stanford.edu, Phone: +1 650 723-5711.

Authorship Contributions: AF made substantial contributions to the design and conception, data analysis and interpretation, drafting the manuscript, critical revision of the manuscript, and final approval. VYC made substantial contributions to data interpretation, drafting the manuscript, critical revision of the manuscript, and final approval. KPV and DRD made substantial contributions to the conception and design, critical revision of the manuscript, and final approval. JK and OC made substantial contributions to data analysis, drafting the manuscript, critical revision of the manuscript, and final approval.

Statement of Financial Support:
AF was supported by Eunice Kennedy Shriver National Institute of Child Health and Human Development (K23HD079557) for this work.

Disclosures: AF is a scientific consultant for Takeda Pharmaceuticals unrelated to this work. DRD is a scientific consultant for Masimo Corporation and AbbVie Inc unrelated to this work. The other authors have no conflicts of interest to disclose.

Category of study: Clinical research article

Consent Statement: Informed consent was obtained for patients in the prospective study. A waiver of consent was granted for the retrospective study.

Results: Birth weight was a significant predictor of theophylline clearance and volume of distribution ($p<0.05$). The median half-life was 39.5 h (range 27.2 to 50.4). An aminophylline loading dose of 7 mg/kg followed by 1.6 mg/kg q12h was predicted to achieve target concentrations in 84% of simulated neonates.

Conclusions: In neonates with HIE undergoing hypothermia, theophylline clearance was low with a 50% longer half-life compared to full-term normothermic neonates without HIE. Dosing strategies need to consider the unique pharmacokinetic needs of this population.

INTRODUCTION

Due to global hypoxic/ischemic insult, acute kidney injury (AKI) is common after birth in neonates with moderate to severe hypoxic ischemic encephalopathy (HIE).(1–3) Theophylline and its salt formulation aminophylline (i.e. theophylline + ethylenediamine in a 2:1 ratio) are non-selective adenosine receptor antagonists that improve renal perfusion in the setting of hypoxia/ischemia(4,5) and may offer therapeutic benefit in neonates with HIE. Several randomized controlled trials (RCTs) in severely asphyxiated neonates have demonstrated a single IV dose of aminophylline or theophylline given within hours after birth reduces the risk of severe renal dysfunction in the first days of life.(6–11) However, all studies were performed in lower or middle income countries, and neonates did not receive concomitant therapeutic hypothermia, which is standard of care in most developed countries. In a contemporary observational cohort of neonates receiving therapeutic hypothermia for HIE, those exposed to theophylline demonstrated increased urine output and a slow decline in serum creatinine, suggesting a beneficial effect even during cooling.(12) However, the benefit of theophylline in neonates with HIE receiving hypothermia remains to be established and its use remains ‘off-label’. As theophylline is advanced as a renal protective therapy, further pharmacokinetic investigation is essential to guide dosing strategies in this vulnerable population.

Theophylline has a narrow therapeutic index, and individualized dosing strategies in a patient population are needed to ensure adequate exposures for efficacy yet avoid high exposures associated with toxicity.(13,14) In older infants and children, theophylline is almost entirely metabolized in the liver via demethylation and hydroxylation. However, in neonates liver metabolism is markedly reduced, and renal elimination of unchanged drug in the urine accounts for 50% of drug elimination.(13) Neonates with HIE receiving hypothermia present an additional challenge from a dosing standpoint due to frequent hypoxic ischemic injury of organs important in drug metabolism and elimination (i.e. liver and kidney) and potential effects of hypothermia itself on drug pharmacokinetics.(15,16) Several previous pharmacokinetic studies in neonates with HIE receiving hypothermia have demonstrated altered pharmacokinetics and unique dose needs for critical medications including morphine, gentamicin, phenobarbital, and midazolam.(17–20) As theophylline is advanced as a renal protective therapy in neonates with HIE receiving hypothermia, an understanding of its pharmacokinetics will be essential to guide dosing.

Theophylline given as its salt formulation, aminophylline, has been used ‘off-label’ at our center for several years in neonates with HIE receiving hypothermia if low urine output

(UOP) and/or rising serum creatinine (SCr) develop. This population provided a unique opportunity to examine the pharmacokinetics of theophylline. Utilizing data collected from (a) therapeutic drug monitoring during clinical care and (b) an opportunistic prospective clinical PK study, we evaluated the population pharmacokinetics of theophylline and developed customized dosing strategies for neonates with HIE receiving hypothermia.

METHODS

General Study Design

We performed a population pharmacokinetic analysis of theophylline given as its ethylenediamine salt form aminophylline in neonates with HIE undergoing therapeutic hypothermia at a single tertiary care neonatal intensive care unit (NICU). Patients who received aminophylline as part of clinical care were enrolled as part of (a) a retrospective chart review or (b) a prospective, opportunistic pharmacokinetic study. The prospective study was part of a larger clinical pharmacokinetic study in neonates <3 months post-natal age admitted to the NICU and receiving aminophylline for renal indications. Both the prospective and retrospective study were approved by the Stanford Institutional Review Board. Informed consent was obtained for all patients in the prospective study.

Patients

Neonates were ≥ 36 weeks gestational age diagnosed with moderate or severe HIE undergoing therapeutic hypothermia. Criteria for hypothermia were as outlined in the National Institute of Child Health and Human Development (NICHD) Whole Body Hypothermia study (21) with a planned duration of hypothermia therapy for 72 hours. Whole body cooling (target temperature 33.5°C) was achieved using either CSZ Blanketrol II/III Hyper-Hypothermia system (Cincinnati SubZero, Cincinnati, Ohio) or CritiCool thermoregulation system (Belmont Medical Technologies, Billerica, MA). Exclusion criteria included: presence of anatomical renal anomaly based on postnatal evaluation of the patient; need for renal replacement therapy; or major genetic abnormality (trisomy 13, 18 or 21).

Aminophylline Administration and Therapeutic Drug Monitoring

Aminophylline was given as part of standard of care for low urine output (<1 cc/kg/h), rising serum creatinine, and/or other concern for AKI by the treating physician. Aminophylline was given as a loading dose of 5 mg/kg (4 mg/kg theophylline equivalent) intravenous (IV) over 30 minutes followed by 1.8 mg/kg (1.4 mg/kg theophylline equivalent) IV every 6 hours. Theophylline trough levels before the fourth or fifth dose were routinely monitored as part of clinical care and adjusted to maintain a level of 5–7 mg/L. Aminophylline was discontinued at the discretion of the treating physician. Quantitative determination of theophylline serum concentrations during clinical care were performed by the Stanford Clinical Laboratory using a particle enhanced turbidimetric inhibition immunoassay, PETINIA (Dimension clinical chemistry system, Siemens Healthcare Diagnostics Inc., Newark, DE). The lower limit of quantification was 0.2 mg/L. The within-run and total coefficient of variation for the assay were less than 5%.

Pharmacokinetic Sampling in Prospective Study

In neonates enrolled in the prospective clinical study, dried blood spot (DBS) samples for pharmacokinetic analysis were collected at two different time periods while receiving aminophylline. Period 1 was on day 1 to 2 of aminophylline, and period 2 was on day 3 to 5 of aminophylline. In both periods, DBS samples were collected onto Whatman 903 Protein Saver Cards (GE Health Care Life Sciences from Fisher Scientific, Fair Lawn, NJ) at the following times relative to a dose: pre-dose, 0.75–2h, 2–4h, and 4–6h. Samples were collected around the same dose for a given period.

For each DBS sample, ~100 μL whole blood was collected on Whatman 903 filter paper cards (~50 μL whole blood/spot × 2 spots) from an in-dwelling catheter already in place for clinical care or from a venous sample collected at the same time as laboratories for clinical care. After allowing to air dry for 4–24 hours, the DBS sample was then stored between −70 and −80° C until analysis. The concentrations of theophylline in the DBS were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay by iC42 Clinical Research and Development (Aurora, CO, USA). The lower limit of quantification was 0.05 mg/L and the calibration curves were linear from 0.05 mg/L to 7.5 mg/L (r^2>0.99). Samples were diluted 1:5 if above the upper limit of quantification and re-run. The assay was validated and considered fit for purpose. For details of the methods and validation see ‘Electronic Supplementary Material.’

Population Pharmacokinetic Analysis

A population pharmacokinetic model was developed from the theophylline concentration time data using the nonlinear mixed-effects modeling program NONMEM (Version 7.3, Icon Development Solutions, Ellicott City, MD). Aminophylline dose was converted to theophylline equivalents by multiplying by 0.79. Standard model building and evaluation methods were used as previously described and included goodness-of-fit plots, bootstrap resampling techniques, and simulation-based diagnostics.(22) In brief, after developing the structural model (i.e. one compartment model with linear elimination), the effect of weight on clearance and volume was implemented *a priori* using an allometric model with the exponent defining the relationship fixed to 0.75 and 1, respectively.(23) Clinically plausible covariates were evaluated in the model in a stepwise forward addition, backward elimination procedure and included gestational age (GA), postnatal age (PNA), serum creatinine (SCr), period of hypothermia treatment, and disease severity markers (inotropic support, invasive ventilatory support, acute kidney injury, and electrographic or clinical seizures). Acute kidney injury was defined based on a rise in SCr of 0.3 mg/dL or 50% from the lowest previous value.(24) Significance was set at $p<0.001$ during model selection. DBS concentrations (C_{DBS}) were adjusted to plasma concentrations ($C_{plasma,adjusted}$) in the model based on the hematocrit of the neonate and a model estimated red blood cell-to-plasma ratio of theophylline.(25) Additional model development details are available in the ‘Electronic Supplementary Material.’

Exposure Response Analysis

The relationship between the average theophylline plasma concentration over 24 hours ($C_{avg,24}$) and change in urine output (ΔUOP) over the 24 hours after aminophylline start was

examined testing both linear and log-linear relationships. UOP over the 12 hours before aminophylline served as baseline for each neonate. $C_{avg,24}$ was calculated in each neonate in NONMEM using the final PK model by integrating the theophylline concentration over the first 24 hours and then dividing by 24. Similarly, the relationship between $C_{avg,24}$ and change in serum creatinine (ΔSCr) at 48 hours after aminophylline start was examined.

Development of Optimized Dose

To optimize aminophylline dosing regimens in neonates with HIE undergoing therapeutic hypothermia Monte Carlo simulations were conducted. Using the final population pharmacokinetic model parameters estimates, the pharmacokinetic profiles of 3,000 'hypothetical' neonates with birth weights of 2.5, 3.5 and 4.5 kg were repeatedly simulated. Loading doses examined ranged from 5 to 10 mg/kg given intravenous over 30 minutes. 'Maintenance' doses examined ranged from 1 to 2 mg/kg given every 6 or 12 hours. A trough serum concentration between 4 – 10 mg/L was targeted based on prior clinical reports in adults, children, and neonates showing these exposures are safe and associated with improvement in UOP or serum creatinine (26–31). In addition, to avoid toxicity in these vulnerable neonates serum concentrations considered potentially toxic (i.e. > 10 mg/L) were also examined.(13) The dosing strategy that resulted in the highest targeted achievement rate was selected. Statistical analyses of the data and figure productions were performed using R version 2.12 (R core team) and STATA 13 (StataCorp LP, College Station, TX).

RESULTS

Patients and Theophylline Concentrations

Twenty-two neonates with HIE treated with hypothermia had theophylline concentration data available for analysis. Five patients were enrolled in the prospective PK study and 17 neonates in the retrospective chart review. Patient characteristics are shown in Table 1. Of neonates studied, 17 (77%) had seizures, 14 (64%) required inotropic support, and 6 (27%) died after withdrawal of intensive care support during the first week of life for poor neurologic prognosis. Aminophylline was not stopped in any neonate due to concern for toxicity.

Patients were started on aminophylline at a median (IQR) age of 28 (16 – 38) hours after birth, and the median (IQR) duration of aminophylline treatment was 63 (36 – 94) hours. All patients received a loading dose between 4.7 to 5.1 mg/kg except one who received a dose of 2.8 mg/kg. Starting maintenance doses were between 1.7 to 1.9 mg/kg every 6 hours in all patients except for one patient who received 2.4 mg/kg every 6 hours and one patient who received 1.0 mg/kg every 6 hours.

There were 52 plasma theophylline concentrations measured as part of clinical care in the 22 study patients, and an additional 29 DBS theophylline concentrations measured in the 5 patients enrolled in the prospective PK study. This resulted in a total of 81 theophylline concentrations available for pharmacokinetic analysis. The number of concentrations measured on the 1^{st}, 2^{nd}, 3^{rd}, and $\geq 4^{th}$ day of therapy were 30, 18, 23 and 10, respectively. The number of concentrations measured <2 h, 2–4h, and >4 h after the last dose were 16, 12

and 53, respectively. No theophylline concentrations measured by either method were below the limit of quantification.

Population Pharmacokinetic Analysis

The time course of theophylline concentration data was adequately described by a one-compartment model with first-order elimination and an exponential error model for inter-patient variability on clearance and volume. The residual variability was best described by separate proportional error models for plasma samples and DBS samples. After the addition of birth weight to the model, no other significant predictors of clearance or volume were identified.

The final population pharmacokinetic model parameter estimates are presented in Table 2. The mean (range) of pharmacokinetic parameters estimates in the 22 study patients were a clearance 0.049 L/h (0.030 – 0.093), volume 2.7 L (1.9–4.0), and half-life 39.2 hours (27.2 – 50.4).

Diagnostic evaluation of the final model demonstrated no systemic bias (Figure 1; Supplemental Figure S1, online), and parameter estimates as found by a bootstrap resampling technique were in agreement with those obtained by the final population pharmacokinetic model (Table 2). Simulation based diagnostics using normalized prediction distribution errors (NPDE)(32,33) demonstrated that the final model performed well in describing the observed data. The NPDE mean was 0.07 (95% CI: −0.16 to 0.30) and variance was 1.07 (95% CI: 0.76 – 1.37); the theoretical NPDE mean is zero with a variance 1.0. The percentage of observations that fell inside the theoretical 90% prediction interval were 90.1%. In addition, there were no major trends in NPDE across predicted concentration, time, or birth weight (Supplemental Figure S2, online). The NPDE mean was similar for DBS samples (0.01 [95% CI: −0.44 to 0.46]) and plasma samples (0.1 [95% CI: −0.17 to 0.36]). To evaluate the impact of DBS samples on PK parameter estimates, the final model was re-estimated using only plasma samples, and all parameter estimates were within 10% of the full dataset except the interindividual variability of volume (12.7% lower) and residual variability of plasma samples (20.4% lower).

Exposure Response

Twelve patients had UOP data available for analysis. After aminophylline start, UOP significantly increased from 0.7 ± 0.5 ml/kg/h to 3.2 ± 1.6 ml/kg/h (Δ 2.6 ± 1.5 ml/kg/h; $p<0.001$). No relationship between $C_{avg,24}$ and ΔUOP was found (Figure 2a, $p=0.70$). All patients had SCr data available. No significant change in SCr was seen 48 h after aminophylline start (1.2 ± 0.4 mg/dL vs 1.1 ± 0.6 mg/dL; $p=0.37$), and no relationship between $C_{avg,24}$ and ΔSCr was found (Figure 2b, $p=0.36$).

Dose Optimization

Drug accumulation occurred with the aminophylline dosing strategy used in clinical care (5 mg/kg load followed by 1.8 mg/kg every 6h), and 10 of 11 (91%) neonates who had drug concentrations measured after 48 hours of treatment had a theophylline concentration ≥ 10 mg/L. This was also seen in Monte Carlo simulations with 90% of simulated neonates

predicted to have a trough concentration at steady-state ($C_{trough,ss}$) >10 mg/L with the dosing strategy used in clinical care (Figure 3a). The optimal aminophylline dose found from Monte Carlo simulations was a load of 7 mg/kg followed by 1.6 mg/kg every 12h (Figure 3b). At this dosing strategy, 84% of simulated neonates achieved the target $C_{trough,ss}$ between 4–10 mg/L, and 9% had a $C_{trough,ss}$ >10 mg/L.

DISCUSSION

This is the first study to describe the pharmacokinetics of theophylline in neonates with HIE receiving hypothermia. The major study finding was that theophylline clearance is low in neonates with HIE receiving hypothermia, resulting in a >50% longer half-life compared to what is reported in the FDA theophylline prescribing information for term neonates.(13) Theophylline (or aminophylline) dosing strategies will need to consider the unique pharmacokinetics of this vulnerable population. In addition, monitoring of drug concentrations will be necessary due to the narrow therapeutic window of theophylline and the underlying variation in pharmacokinetics between neonates with HIE receiving hypothermia.

An understanding of the pharmacokinetics of a drug are fundamental to developing safe and effective dosing strategies. In the current study we examined the population pharmacokinetics of theophylline in neonates with HIE receiving hypothermia. For a typical study neonate with HIE receiving hypothermia, theophylline clearance was 14.5 ml/h/kg. No clearance for comparison in term neonates is reported in the literature as historically theophylline has primarily been used in preterm neonates as a treatment for apnea of prematurity. The FDA prescribing information for theophylline does report a half-life of 25.7 hours for term neonates 1–2 days old, which when compared to the half-life of 39.2 hours found in the current study suggests a markedly lower clearance in neonates with HIE receiving hypothermia(13). Reduced drug clearance in neonates with HIE ± hypothermia has also been found for several other drugs when compared to nonasphyxiated neonates of the same gestational age.(17–20,34)

Two prior reports compared the pharmacokinetics of theophylline in asphyxiated and nonasphyxiated preterm neonates and found a 19%(35) and 46%(36) lower clearance in the asphyxiated group. These preterm neonates were not cooled. Interestingly, the clearance of theophylline we found in term neonates with HIE receiving hypothermia was within the range reported in asphyxiated preterm neonates (10.8 ml/h/kg(36) and 16.4 ml/h/kg(35)). A decrease in clearance of theophylline in term neonates with HIE receiving hypothermia may be due in part to organ dysfunction, changes in blood flow, the effect of hypothermia, and/or other unknown factors.(15,16) In our study, markers of disease severity (inotropic support, invasive ventilatory support, acute kidney injury, and/or seizures) and hypothermia were examined and not found to be predictors of clearance. However, our study likely had low power to detect predictors of clearance given the small sample size and lack of a control group. The volume of distribution of theophylline in term neonates with HIE receiving hypothermia (0.82 L/kg) was similar to prior reports in preterm neonates (0.69 – 0.86 L/kg).(36–39)

The mechanism by which theophylline provides renal protection in the setting of hypoxia ischemia is thought to be via its properties as a non-selective adenosine receptor antagonist. During renal hypoxia, adenosine levels increase due to adenosine triphosphate (ATP) consumption exceeding production. Subsequent adenosine A_1 receptor mediated vasoconstriction occurs in the afferent arteriole of the renal cortex(40,41) leading to a reduction in renal blood flow and glomerular filtration rate (GFR) in newborn animal models of hypoxemia (4). If adenosine receptors are inhibited with intravenous theophylline in the setting of hypoxemia, renal blood flow, GFR, and filtration fraction are preserved.(4,5) The concentration of theophylline effective in the newborn animal model was ~0.7 mg/L(4). This effective concentration is in line with *in vitro* binding affinity studies demonstrating adenosine receptor inhibition at theophylline concentrations of 1–2 mg/L (42–44). Similarly, clinical studies of theophylline in neonates, children, and adults demonstrated augmented urine output or improved creatinine clearance at concentrations of 4–10 mg/L.(26–29) In our study, the average theophylline concentration in neonates during the first day of treatment ranged from 4.9–8.6 mg/L and resulted in a clinically significant increase in UOP. Within this concentration range, no relationship between theophylline exposure and change in UOP were observed. Similarly, no relationship between theophylline concentration and serum creatinine was found. The lack of an exposure-response relationship may potentially be due to neonates being within a range of exposures where maximal response was already achieved. Based on animal and *in vitro* binding affinity studies described above, lower concentrations in neonates might be effective yet have not been studied. While the optimal theophylline exposure for renal protective effects in neonates with HIE receiving hypothermia is not currently known, evidence to date support clinically effective target concentrations of 4 to 10 mg/L.

Applying the final population pharmacokinetic model, Monte Carlo simulations were performed to optimize the aminophylline dosing strategy most likely to achieve target theophylline concentrations of 4 to 10 mg/L in neonates with HIE receiving hypothermia. The optimal aminophylline loading dose of 7 mg/kg (= theophylline dose 5.5 mg/kg) followed by 1.6 mg/kg (= theophylline dose 1.3 mg/kg) every 12 hours achieved target concentrations at steady-state in 84% of neonates. In comparison, the dosing strategy used during clinical care at time of the study was a 2-fold higher daily dose (7.2 mg/kg/day vs. 3.2 mg/kg/day) and was predicted to result in high concentrations (>10 mg/L) at steady-state in 90% of neonates. Due to the long half-life of theophylline, high exposures resulting from a dosing strategy may not be recognized for several days as drug accumulation occurs (Figure 2a). In our patients, concentrations of theophylline measured on the first day of treatment were within the target range in all but one neonate, but in the 11 who remained on aminophylline for more than 48 hours, 10 (91%) had subsequent concentrations >10 mg/L. While these higher concentrations were not associated with known adverse outcomes compared to neonates with HIE who did not receive aminophylline(12), assessment of toxicity is difficult in this population who frequently have multi-organ failure including central nervous system derangements and seizures.(16) Our center has since implemented in clinical care the optimized dosing strategy supported by this study. In addition, theophylline trough concentrations are monitored before the fourth maintenance dose. However, ongoing safety assessment within well-controlled studies will be important.

This study is limited by the small sample size and caution is warranted generalizing our results across a heterogenous population of neonates with HIE receiving hypothermia. Our center's use of aminophylline provided a unique opportunity, and we utilized an opportunistic design to examine neonates already receiving aminophylline as part of clinical care. Neonates in our study are likely representative of other neonates with HIE receiving hypothermia as eligibility criteria is based on standardized guidelines from the NICHD clinical trials demonstrating clinical efficacy of hypothermia.(21) We have applied this same opportunistic approach to study gentamicin(17) and morphine(18) pharmacokinetics successfully in neonates with HIE receiving hypothermia, and our findings were later confirmed in pharmacokinetic studies performed by other centers.(45,46)

Micro-volume pharmacokinetic sampling using DBS in the prospective study minimized blood volume requirements and enabled more sampling in each neonate.(47) A limitation resulting from the use of DBS sampling is the red blood cell-to-plasma ratio for theophylline is not currently known, and this ratio is important to help standardize concentrations in DBS samples compared to plasma samples. Since the red blood cell-to-plasma ratio was not known, it was estimated within the underlying pharmacokinetic model. This approach resulted in a final pharmacokinetic model that was able to adequately predict concentrations in both DBS and plasma samples. In addition, a sensitivity analysis demonstrated minimal changes in the predicted pharmacokinetics of theophylline when only plasma samples were used to estimate the final model.

Future research is critical to establish the clinical utility of aminophylline (and/or theophylline) for renal protection in neonates with HIE. While the pharmacokinetic data acquired here will help with design of a randomized controlled trial, a greater understanding of the importance of the timing of aminophylline administration in relation to hypoxic ischemic injury, the duration of exposure required to optimize efficacy, and populations most likely to benefit from treatment is needed. Aminophylline will also need to be studied in conjunction with more precise and dynamic biomarkers of renal function and injury beyond urine output and creatinine.(48) Lastly, demonstrating the long term impact of treatment on kidney function or other relevant clinical outcomes beyond the intensive care setting will be necessary to change clinical practice.

Conclusions

Pharmacokinetic studies are essential to support the clinical development of novel therapies in neonates and provide a starting point to guide safe and effective dosing strategies. In neonates with HIE receiving hypothermia, theophylline clearance was low with a 50% longer half-life compared to full-term neonates without HIE not undergoing hypothermia. Accordingly, customized dosing strategies are needed in this population, and an aminophylline loading dose of 7 mg/kg (= theophylline dose 5.5 mg/kg) followed by 1.6 mg/kg (= theophylline dose 1.3 mg/kg) every 12 hours was predicted to regularly achieve theophylline concentrations associated with renal pharmacodynamic effects. Randomized controlled trials are needed in neonates with HIE receiving hypothermia to better establish the role of aminophylline (or theophylline) as a renal protective therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. Selewski DT, Jordan BK, Askenazi DJ, Dechert RE, Sarkar S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. J Pediatr 2013;162:725–729.e1. [PubMed: 23149172]
2. Kirkley MJ et al. Acute kidney injury in neonatal encephalopathy: an evaluation of the AWAKEN database. Pediatr Nephrol 2019;34:169–76. [PubMed: 30155763]
3. Gupta C, Massaro AN, Ray PE. A new approach to define acute kidney injury in term newborns with hypoxic ischemic encephalopathy. Pediatr Nephrol 2016;31:1167–78. [PubMed: 26857710]
4. Gouyon JB, Guignard JP. Theophylline prevents the hypoxemia-induced renal hemodynamic changes in rabbits. Kidney Int 1988;33:1078–83. [PubMed: 3404810]
5. Osswald H, Gleiter C, Mühlbauer B. Therapeutic use of theophylline to antagonize renal effects of adenosine. Clin Nephrol 1995;43 Suppl 1:S33–37. [PubMed: 7781203]
6. Jenik AG et al. A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. Pediatrics 2000;105:E45. [PubMed: 10742366]
7. Bakr AF. Prophylactic theophylline to prevent renal dysfunction in newborns exposed to perinatal asphyxia--a study in a developing country. Pediatr Nephrol 2005;20:1249–52. [PubMed: 15947981]
8. Bhat MA, Shah ZA, Makhdoomi MS, Mufti MH. Theophylline for renal function in term neonates with perinatal asphyxia: a randomized, placebo-controlled trial. J Pediatr 2006;149:180–4. [PubMed: 16887430]
9. Eslami Z, Shajari A, Kheirandish M, Heidary A. Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia. Iran J Kidney Dis 2009;3:222–6. [PubMed: 19841526]
10. Raina A, Pandita A, Harish R, Yachha M, Jamwal A. Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates. Acta Paediatr 2016;105:e448–451. [PubMed: 27173369]
11. Saboute M et al. Effect of Aminophylline in Preventing Renal Dysfunction among Neonates with Prenatal Asphyxia: A Clinical Trial. Arch Iran Med 2020;23:312–8. [PubMed: 32383615]
12. Chock VY, Cho S-H, Frymoyer A. Aminophylline for renal protection in neonatal hypoxic-ischemic encephalopathy in the era of therapeutic hypothermia. Pediatr Res 2020;
13. Hospira, Inc. FDA package insert aminophylline (aminophylline injection, solution). 2009;
14. Lowry JA, Jarrett RV, Wasserman G, Pettett G, Kauffman RE. Theophylline toxicokinetics in premature newborns. Arch Pediatr Adolesc Med 2001;155:934–9. [PubMed: 11483122]
15. Zanelli S, Buck M, Fairchild K. Physiologic and pharmacologic considerations for hypothermia therapy in neonates. J Perinatol 2011;31:377–86. [PubMed: 21183927]
16. O'Dea M et al. Management of Multi Organ Dysfunction in Neonatal Encephalopathy. Front Pediatr 2020;8:239. [PubMed: 32500050]
17. Frymoyer A, Meng L, Bonifacio SL, Verotta D, Guglielmo BJ. Gentamicin pharmacokinetics and dosing in neonates with hypoxic ischemic encephalopathy receiving hypothermia. Pharmacotherapy 2013;33:718–26. [PubMed: 23553582]
18. Frymoyer A et al. Decreased Morphine Clearance in Neonates With Hypoxic Ischemic Encephalopathy Receiving Hypothermia. J Clin Pharmacol 2017;57:64–76. [PubMed: 27225747]
19. Welzing L et al. Disposition of midazolam in asphyxiated neonates receiving therapeutic hypothermia--a pilot study. Klin Padiatr 2013;225:398–404. [PubMed: 24288267]
20. Gal P, Toback J, Erkan NV, Boer HR. The influence of asphyxia on phenobarbital dosing requirements in neonates. Dev Pharmacol Ther 1984;7:145–52. [PubMed: 6723489]
21. Shankaran S et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574–84. [PubMed: 16221780]

22. Frymoyer A, Juul SE, Massaro AN, Bammler TK, Wu YW. High-dose erythropoietin population pharmacokinetics in neonates with hypoxic-ischemic encephalopathy receiving hypothermia. Pediatr Res 2017;81:865–72. [PubMed: 28099423]
23. Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32. [PubMed: 17914927]
24. Jetton JG et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health 2017;1:184–94. [PubMed: 29732396]
25. Hinderling PH. Red blood cells: a neglected compartment in pharmacokinetics and pharmacodynamics. Pharmacol Rev 1997;49:279–95. [PubMed: 9311024]
26. Mazkereth R et al. Effects of theophylline on renal function in premature infants. Am J Perinatol 1997;14:45–9. [PubMed: 9259896]
27. Tamburro RF et al. A prospective assessment of the effect of aminophylline therapy on urine output and inflammation in critically ill children. Front Pediatr 2014;2:59. [PubMed: 24971305]
28. Lynch BA et al. Low-dose aminophylline for the treatment of neonatal non-oliguric renal failure-case series and review of the literature. J Pediatr Pharmacol Ther 2008;13:80–7. [PubMed: 23055869]
29. Dai B et al. Effect of theophylline on prevention of contrast-induced acute kidney injury: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2012;60:360–70. [PubMed: 22516682]
30. Axelrod DM et al. Initial experience using aminophylline to improve renal dysfunction in the pediatric cardiovascular ICU. Pediatr Crit Care Med 2014;15:21–7. [PubMed: 24212284]
31. Bell M, Jackson E, Mi Z, McCombs J, Carcillo J. Low-dose theophylline increases urine output in diuretic-dependent critically ill children. Intensive Care Med 1998;24:1099–105. [PubMed: 9840247]
32. Brendel K, Comets E, Laffont C, Mentré F. Evaluation of different tests based on observations for external model evaluation of population analyses. J Pharmacokinet Pharmacodyn 2010;37:49–65. [PubMed: 20033477]
33. Comets E, Brendel K, Mentré F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. Comput Methods Programs Biomed 2008;90:154–66. [PubMed: 18215437]
34. van den Broek MPH et al. Pharmacokinetics and clinical efficacy of phenobarbital in asphyxiated newborns treated with hypothermia: a thermopharmacological approach. Clin Pharmacokinet 2012;51:671–9. [PubMed: 23018530]
35. Gilman JT, Gal P, Levine RS, Hersh CB, Erkan NV. Factors influencing theophylline disposition in 179 newborns. Ther Drug Monit 1986;8:4–10. [PubMed: 3961896]
36. Gal P, Boer HR, Toback J, Wells TJ, Erkan NV. Effect of asphyxia on theophylline clearance in newborns. South Med J 1982;75:836–8. [PubMed: 7089654]
37. Moore ES, Faix RG, Banagale RC, Grasela TH. The population pharmacokinetics of theophylline in neonates and young infants. J Pharmacokinet Biopharm 1989;17:47–66. [PubMed: 2715932]
38. Aranda JV, Sitar DS, Parsons WD, Loughnan PM, Neims AH. Pharmacokinetic aspects of theophylline in premature newborns. N Engl J Med 1976;295:413–6. [PubMed: 934239]
39. du Preez MJ, Botha JH, McFadyen ML, Holford NH. The pharmacokinetics of theophylline in premature neonates during the first few days after birth. Ther Drug Monit 1999;21:598–603. [PubMed: 10604818]
40. Fredholm BB. Adenosine, an endogenous distress signal, modulates tissue damage and repair. Cell Death Differ 2007;14:1315–23. [PubMed: 17396131]
41. Hansen PB et al. Vasoconstrictor and vasodilator effects of adenosine in the mouse kidney due to preferential activation of A1 or A2 adenosine receptors. J Pharmacol Exp Ther 2005;315:1150–7. [PubMed: 16120812]
42. Kim S-A et al. Structure-activity relationships at human and rat A2B adenosine receptors of xanthine derivatives substituted at the 1-, 3-, 7-, and 8-positions. J Med Chem 2002;45:2131–8. [PubMed: 12014951]

43. Klotz KN et al. Comparative pharmacology of human adenosine receptor subtypes - characterization of stably transfected receptors in CHO cells. Naunyn Schmiedebergs Arch Pharmacol 1998;357:1–9. [PubMed: 9459566]

44. Jacobson KA, Ijzerman AP, Linden J. 1,3-dialkylxanthine derivatives having high potency as antagonists at human A2B adenosine receptors. Drug Development Research 1999;47:45–53.

45. Favié LMA et al. Pharmacokinetics of morphine in encephalopathic neonates treated with therapeutic hypothermia. PLoS ONE 2019;14:e0211910. [PubMed: 30763356]

46. Bijleveld YA et al. Altered gentamicin pharmacokinetics in term neonates undergoing controlled hypothermia. Br J Clin Pharmacol 2016;81:1067–77. [PubMed: 26763684]

47. Clavijo CF et al. A sensitive assay for the quantification of morphine and its active metabolites in human plasma and dried blood spots using high-performance liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem 2011;400:715–28. [PubMed: 21400080]

48. Basu RK. Dynamic Biomarker Assessment: A Diagnostic Paradigm to Match the AKI Syndrome. Front Pediatr 2019;7:535. [PubMed: 32039106]

Impact

- Theophylline is potential renal protective therapy in neonates with HIE undergoing therapeutic hypothermia, however the pharmacokinetics and dose needs in this population are not known.
- Theophylline clearance was low in neonates with HIE undergoing therapeutic hypothermia with a 50% longer half-life compared to full-term normothermic neonates without HIE.
- As theophylline is advanced in clinical development, dosing strategies will need to consider the unique pharmacokinetic needs of neonates with HIE undergoing therapeutic hypothermia.

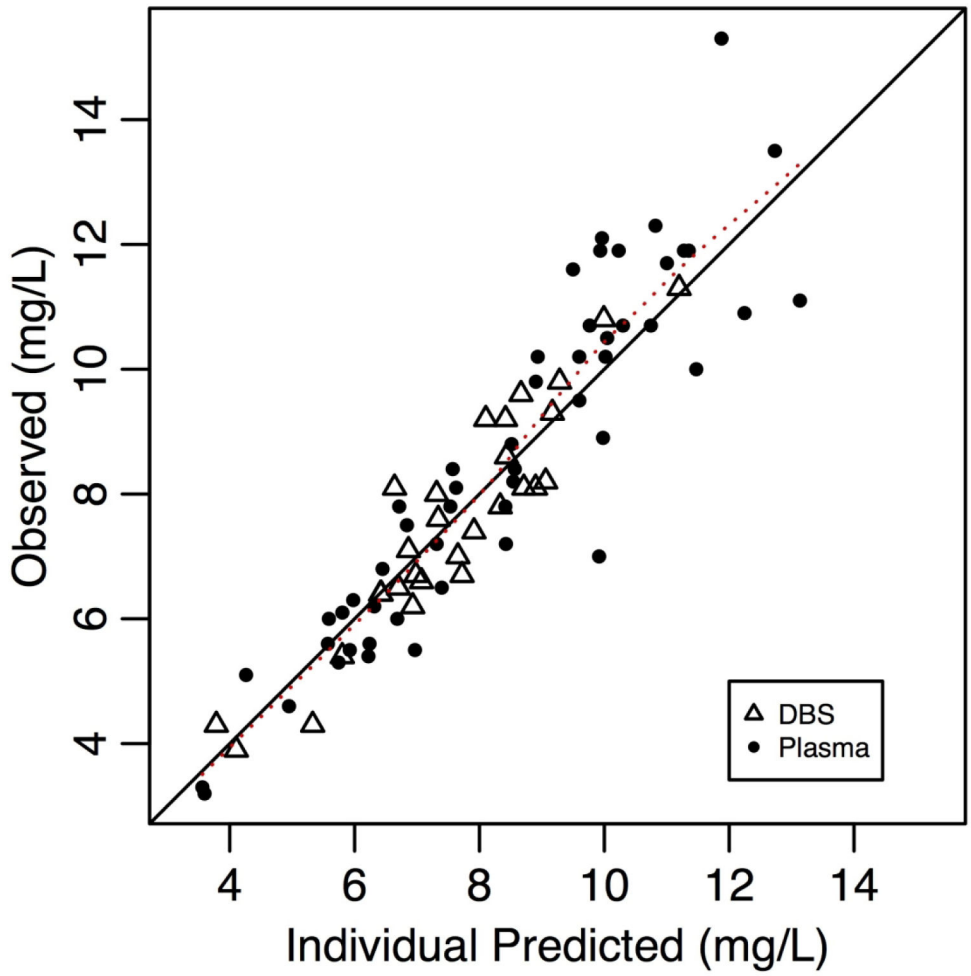

Figure 1.

Individual predicted theophylline concentrations in neonates with HIE receiving hypothermia based on the final pharmacokinetic model as compared to the observed measured concentrations. DBS, dried blood samples measured as part of prospective study; Plasma, plasma samples measured as part of clinical care.

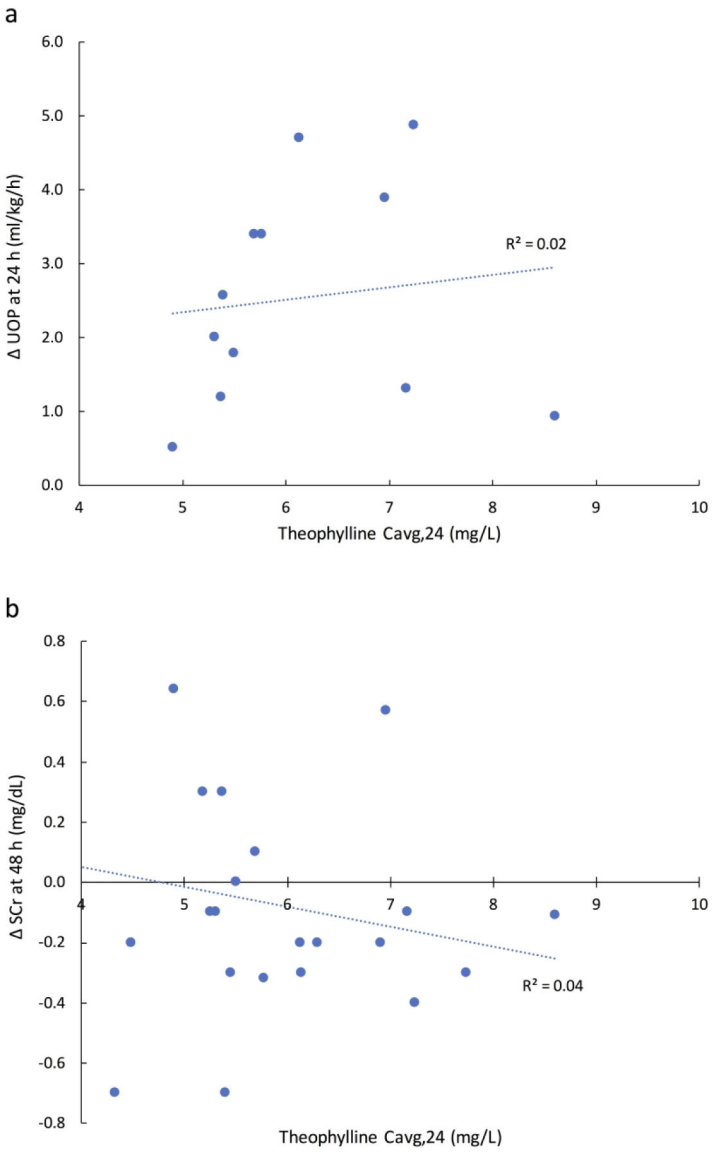

Figure 2.

Relationship between the average theophylline concentration over the first 24 hours of treatment ($C_{avg,24}$) and a) change in urine output (ΔUOP) 24 hours after start of treatment and b) change in serum creatinine (ΔSCr) 48 hours after start of treatment.

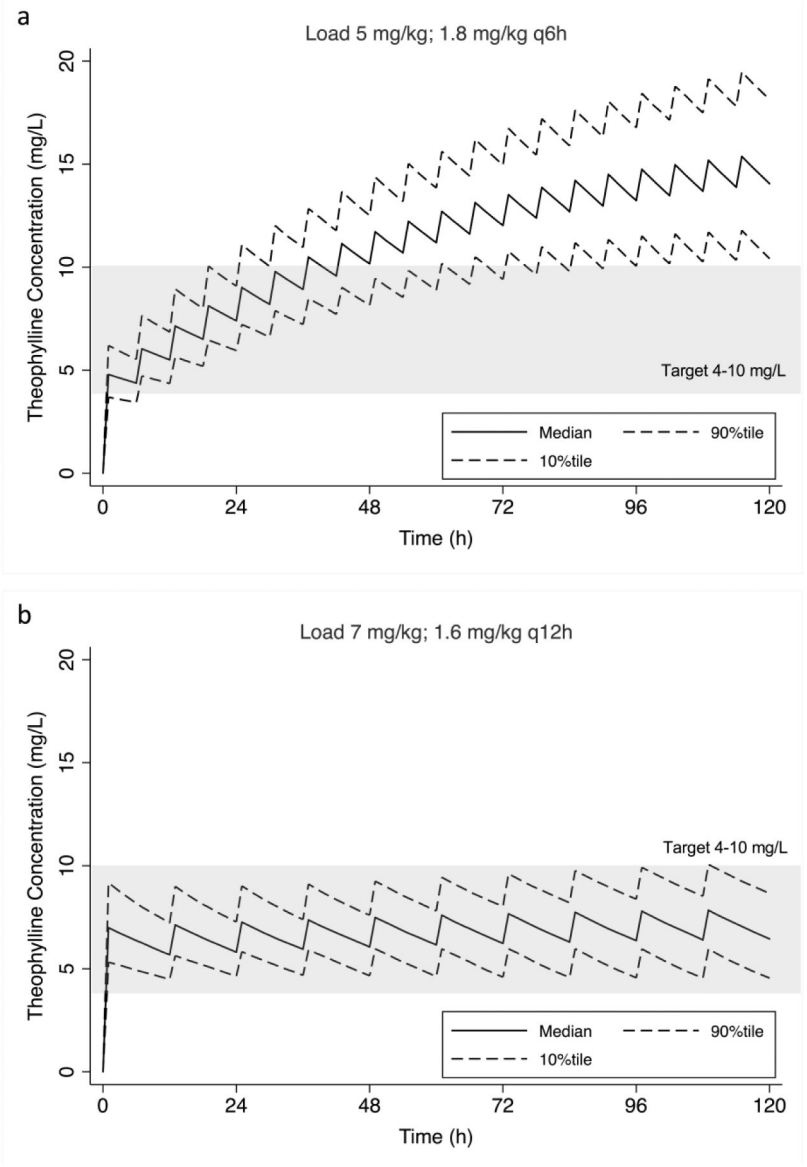

Figure 3.

Predicted theophylline concentration-time course after aminophylline using a) dosing strategy used in clinical care during the study time period (loading dose 5 mg/kg followed by 1.8 mg/kg every 6 hours) and b) optimized dosing strategy (loading dose 7 mg/kg followed by 1.6 mg/kg every 12 hours). Each dosing strategy was simulated in 3000 neonates using the final population pharmacokinetic model. Solid line represents the median and dashed lines represent the 10^{th} and 90^{th} percentile. Shaded area represents targeted concentration range of 4 to 10 mg/L.

Table 1.

Patient Demographics (n = 22)

	Mean ± SD or No.	Min, Max
Gestational Age, wks	38.5 ± 1.8	35.4 – 40.9
Birthweight, kg	3.3 ± 0.5	2.47 – 4.73
Female, n (%)	9 (41%)	
Serum Cr, mg/dL	1.1 ± 0.4	0.5 – 2.1
Hematocrit[a], (%)	49.9 ± 6.0	42.9 – 58.2
Acute kidney injury[b], n (%)	7 (32%)	-
Seizures, n (%)	17 (77%)	-
Inotropic support n (%)	14 (64%)	-
Death, n (%)	6 (27%)	-

Serum Cr, serum creatinine at start of aminophylline

[a]Data for five patients who had dried blood spot sampling

[b]Based on serum creatinine by modified KDIGO criteria for neonates.

Table 2.

Final population PK model parameter estimates for theophylline.[1]

	Final Model		Bootstrap (n=1000)	
Population PK Parameters	**Estimate**	**%SE**	**Median**	**95% CI**
CL (L/h for 3.3 kg)[2]	0.048	9.6%	0.048	0.040 – 0.060
V (L per 3.3 kg)[3]	2.70	5.6%	2.68	2.38 – 3.00
K (RBC/plasma ratio)[4]	0.68	19.4%	0.66	0.42 – 0.98
Interindividual variability				
CL, %CV	25.0%	54.9%	23.3	0.4% – 53.5%
V, %CV	20.5%	37.4%	19.1	0.6% – 27.4%
Residual variability				
DBS, %CV	10.3%	37.0%	10.3	5.8 – 17.1
Plasma, %CV	14.3%	35.9%	13.5	7.9 – 19.2

CL, clearance; V, volume of distribution; %CV, coefficient of variation x 100; %SE, relative standard error x 100; 95% CI, Bootstrap parameter estimate at the 2.5th and 97.5th percentiles; DBS, dried blood spot concentration; HCT, hematocrit; K, red blood cell to plasma ratio

[1], Parameters for theophylline. Aminophylline dose should be converted to theophylline equivalents by multiplying by 0.79.

[2], $\mathrm{CL}_{(\mathrm{L/H})} = 0.048 \times \left(\frac{\mathrm{Birthweight}}{3.3\ \mathrm{kg}}\right)^{0.75}$

[3], $\mathrm{V}_{(\mathrm{L})} = 2.70 \times \left(\frac{\mathrm{Birthweight}}{3.3\ \mathrm{kg}}\right)$

[4], $\mathrm{Predicted\,Concentration}_{(\mathrm{Plasma,\ mg/L})} = \left(\frac{\mathrm{Concentration}_{(\mathrm{DBS,\ mg/L})}}{1 - \mathrm{HCT}(1 - \mathrm{K})}\right)$