JPPT | Pharmacokinetic Modelling Study

Optimal Dosing Recommendations of Clonidine in Pediatrics Using Physiologically Based Pharmacokinetic Modeling

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OBJECTIVE Clonidine has been widely used in the pediatric population to treat neonatal abstinence syndrome (NAS), attention deficit hyperactivity disorder (ADHD), sedation, and Tourette's syndrome; however, there is no consensus on dosing. This research aims to recommend optimal dosing of clonidine in the pediatric population using physiologically based pharmacokinetic (PBPK) modeling.

METHODS The pediatric PBPK model was developed from an adult model by scaling the clearance processes from adults to pediatrics using ontogeny equations. The adult and pediatric models were verified using clinical PK data, and the model performance was evaluated based on visual predictive checks and absolute fold error (AFE). The final pediatric PBPK model was used to simulate clonidine PK in the virtual pediatric population. The optimal dose was recommended based on a target concentration representing clonidine's α-2 central agonist activity (EC_{50} = 40.5 nM).

RESULTS The adult and pediatric models predicted well, with more than 90% of observed data captured within the 95% prediction interval of simulated data. The AFE values were within 2-fold for clonidine plasma concentrations from observed and predicted data. The pediatric simulations showed that 30 µg/kg dose orally for neonates and 0.9 mg/day orally for children (6–17 years) are optimal for achieving target concentrations for maximal α-2 adrenergic activity.

CONCLUSIONS The pediatric PBPK model of clonidine scaled from the adult PBPK model provided optimal dosing recommendations for clonidine in different pediatric age groups. The pediatric PBPK model described in this study can be extended to other pediatric age groups and routes of administration.

ABBREVIATIONS ADHD, attention deficit hyperactivity disorder; ADME, absorption, distribution, metabolism, and elimination; AFE, absolute fold error; C_{max}, maximum plasma concentration; CYP, cytochrome p450; EC_{50}, half maximal effective concentration; NAS, neonatal abstinence syndrome; NOWS, neonatal opioid withdrawal syndrome; PBPK, physiologically based pharmacokinetic; SNS, sympathetic nervous system; SNRIs, selective norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors

KEYWORDS α-2 receptor agonist; attention deficit hyperactivity disorder; clonidine; CYP ontogeny; neonatal abstinence syndrome; physiologically based pharmacokinetic (PBPK) modeling; Tourette's syndrome

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Introduction

Clonidine is a centrally acting α-2 adrenergic receptor agonist used to treat hypertension[1] and substance withdrawal from alcohol, opioids, and smoking in adults.[2] It is also prescribed "off-label" to treat anxiety and insomnia.[3] In pediatrics, it is widely used to treat attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, sedation, neonatal abstinence syndrome (NAS), and neonatal opioid withdrawal syndrome (NOWS).[4–8] Clonidine causes a noticeable improvement in ADHD symptoms but is used less frequently due to adverse effects such as sedation, hypotension, rebound hypertension, and cardiac conduction abnormalities.[9] While not as effective as methylphenidate in treating ADHD, conjunctive use of clonidine is beneficial.[10] The mechanism of action of clonidine in ADHD involves the inhibition of norepinephrine secretion in the brain's prefrontal cortex.[11] This is thought to prevent attention to irrelevant stimuli and improve focused attention. In Tourette's syndrome, extended-release clonidine helps with behavioral and tic symptoms.[12] Though less effective than aripiprazole in clinical trials, it has fewer adverse effects and demonstrates better performance when compared with placebo.[13]

In NAS, clonidine reduces duration of hospital admission with a lower risk of oversedation than

phenobarbital.[14] Since clonidine works at the sympathetic nervous system (SNS) relay point, it can be effective for both NAS and NOWS. However, dosing in these vulnerable patients can be challenging. The required dose relates to the stimulus and the central α-2 adrenergic receptor activation. In NOWS, the SNS traffic may be quite high at the locus coeruleus and require an extremely high α-2 input from clonidine to control it. Using the broader term of NAS, this now includes non-narcotics such as selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs). In addition, NAS may respond differently based on pharmacologic agents.

Clonidine is rapidly absorbed in the blood following oral administration with a bioavailability of ~75.2%. Two hours after oral administration, clonidine reaches its highest concentration in the plasma (C_{max}).[15] It is reasonably soluble in lipids, with a lipophilicity (as represented by log P) of 1.59.[13] The liver metabolizes less than fifty percent of clonidine via CYP2D6, CYP1A2, and CYP3A4 into inactive metabolites. The other 50% of clonidine is excreted in the urine as the unchanged drug and 20% is excreted in the feces.[16] Clonidine's half-life greatly depends on renal function, ranging from between 6 and 23 hours.[16]

Despite wide use of clonidine in pediatrics, its PK across the pediatric age continuum is not well characterized and there is no standardized optimal dosing regimen recommended for clonidine use in pediatrics. This lack of information on optimal clonidine in dosing in pediatrics may be attributed to challenges in conduction traditional PK studies in children.[17] Physiologically based pharmacokinetic (PBPK) modeling is a mathematic modeling technique that integrates drug properties (log P, solubility, protein binding, etc.) and population information (organ size, CYP ontogeny, etc.) to predict the body's response to drugs at various concentrations.[18,19] The ontogeny of CYP enzyme maturation involved in clonidine's metabolism can be incorporated into the PBPK model. When the PBPK model's ability to predict is verified using clinical PK data, several dosing recommendations can be evaluated to elucidate the optimal dosing.

In this study, we initially developed a PBPK model of clonidine in adults and extrapolated it to pediatrics by incorporating CYP enzyme ontogeny equations. The pediatric model was evaluated with clinical data from published clinical studies. The verified pediatric clonidine PBPK model was used to predict the optimal dosing of children across the pediatric age spectrum.

Materials and Methods

Software. The PBPK models were developed with the PK-Sim modeling software (version 9.1), Open Systems Pharmacology Suite (https://www.open-systems-pharmacology.org/). Model input parameter optimization was accomplished using the algorithm implemented into PK-Sim. Clinical data in the scientific literature were digitized using Plot Digitizer (version 2.6.9, https://plotdigitizer.sourceforge.net/).

Development of an Adult PBPK Model. The adult PBPK model was developed and evaluated with observed plasma profiles to assure the reliability of the PBPK model before the model was extrapolated to pediatric populations. A whole-body 15-organ PBPK model implemented in PK-Sim was used for the adult PBPK model.[20] The physicochemical parameters and absorption, distribution, metabolism, and elimination (ADME) data for clonidine were collected from the literature and the DrugBank database.[21,22] The physicochemical and ADME properties used for model development and optimization are provided in Table 1. The physicochemical properties of the drug in the adult PBPK model were optimized using the observed data from clinical studies reporting PK of clonidine after intravenous administration.[23,24] Although clonidine is not usually administered by intravenous route to treat ADHD, Tourette's, NAS, and NOWS, we utilized the intravenous data for initial model verification as it is a standard practice in pediatric PBPK modeling workflow.[25] The model predictions after the optimization of parameters were verified using observed data from clinical studies reporting clonidine PK after oral administration.[26–28] The clinical studies were selected based on the study population, route of administration of clonidine, and the sensitivity of the analytical method used for quantification of clonidine levels in human plasma. The details of the clinical studies from where the observed data sets for model optimization and verification are provided in Table 2. The models were considered acceptable if: 1) at least 80% of observed concentrations were captured within a 90% prediction interval of the predicted concentrations, 2) the average fold error (AFE) values of simulated concentrations were between 0.5 and 2. Clonidine is eliminated approximately 50% by the liver and 50% by the kidneys, so both clearance routes were included in the model. The total hepatic metabolism of clonidine was attributed to the enzymes CYP1A2, CYP2D6, and CYP3A4. The percentage contribution of each CYP enzyme towards the hepatic metabolism of clonidine was: CYP2D6 – 67%, CYP3A4 – 22.2%, and CYP1A2 – 10%. The individual clearances from each enzyme were added to the model to account for the total hepatic metabolism (Table 1).

Pediatric Scaling and Model Applications. The adult clonidine PBPK model, after verification with clinical data, was scaled to pediatrics. The drug-specific parameters, such as physicochemical and ADME properties, were retained in the pediatric model. The population parameters organ size, organ volumes, blood flow, CYP enzyme activity etc., were extrapolated from adults to pediatrics using default ontogeny functions in PK-Sim.[20] The details of the ontogeny functions for the

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enzymes CYP2D6, CYP3A4, and CYP1A2 are provided in the document PK-Sim Ontogeny Database Version 7.3.[29] The final pediatric clonidine PBPK model was verified using the observed data from the published pediatric clinical studies.[30,31] The details of the pediatric clinical studies that were used to generate pediatric PBPK model qualification data sets are provided in Table 3.

Pediatric Dose Optimization Simulations. A virtual pediatric population (N = 1000) of age groups neonates (0 days to 27 days) and ADHD and Tourette's population (6 years through 17 years) were created in PK-Sim. The ADHD and Tourette's population was chosen based on the most common ages at which children are diagnosed with ADHD and Tourette's syndrome. We did not include the population between ages 1 month to 5 years as ADHD and Tourette's are not usually diagnosed in these age groups. The simulations were performed based on commonly reported maximum clonidine dose used to treat ADHD—0.1 to 0.4 mg orally, Tourette's—0.1 to 0.4 mg orally, and NAS—6 µg/kg orally.[13,32–36] However, the reported maximum clonidine dose to treat NAS is based on the studies that used clonidine as an adjunct to opioids.

Assessment of Dose-Exposure Relationship. The mechanism of action of clonidine to treat ADHD, Tourette's syndrome, and NAS is related to a reduction

Table 1. Drug-Specific Parameters Used in PBPK Model Building

Parameter	Literature/ Calculated	Optimized	References
Molecular weight (g/mol)	230.1		21
Compound type	Base		21
LogP	1.59	2.05	
pKa	8.05		
Solubility pH 7.2 (mg/mL)	5		21
Plasma protein	Albumin		21
Fraction unbound (%)	40	48	21
Specific intestinal permeability (cm/min)	1.9×10^{-4}		20
Total hepatic clearance (L/h/kg)*	0.09		22
Individual intrinsic clearances of each CYP enzyme (L/h/kg) CYP2D6 CYP3A4 CYP1A2	 0.06 0.02 0.009		22
Renal clearance (L/h/kg)	0.1		22

PBPK, physiologically based pharmacokinetic

* The total hepatic clearance was partitioned between the enzymes CYP2D6, CYP3A4, and CYP1A2 using their individual intrinsic clearance values.

Table 2. List of Clinical Studies Used in Clonidine Adult PBPK Model Development and Qualification

S. No	Author	Clonidine Dose	Route of Administration	Number of Participants	Bioanalytical Method
Model Development Data Sets					
1	Frisk-Holmberg[23]	275 µg	Intravenous bolus	13	Radioimmunoassay
2	Frisk-Holmberg[24]	0.78–3.36 µg/kg	Intravenous bolus	21	Gas chromatography
Model Verification Data Sets					
3	Anavekar[26]	250 µg	Oral	18	Radioimmunoassay
4	Arndts[27]	75 µg	Oral	7	Radioimmunoassay
5	Wing[28]	300 µg	Oral	5	Gas Chromatography-Mass spectrometry

PBPK, physiologically based pharmacokinetic

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Table 3. Details of Clinical Studies Used in Clonidine Pediatric PBPK Model Qualification

S. No	Author	Clonidine Dose	Route of Administration	Number of Participants	Bioanalytical Method
1	Nielsen[30]	3 µg/kg	Intravenous bolus	21	Liquid Chromatography-Mass Spectroscopy
2	Larsson[31]	4 µg/kg	Oral	8	Liquid Chromatography-Mass Spectroscopy

PBPK, physiologically based pharmacokinetic

of norepinephrine turnover in the central nervous system.[35,37,38] This inhibition of norepinephrine turnover is mediated by clonidine's agonist activity at the α-2A adrenergic receptor, primarily found in the brain's prefrontal cortex. However, the optimal concentration of clonidine that would elicit maximal agonist activity at the α-2A adrenergic receptor in pediatric population is unknown. Gil et al[39] reported that the clonidine is a potent α-2A agonist with an EC50 of 40.5 nM (9.3 ng/mL). Therefore, in this study we used 40.5 nM (9.3 ng/L) as target maximum concentration (C_{max}) of clonidine to ensure efficacy in ADHD and NAS in pediatric population.

Results

Adult PBPK Model Prediction. The adult PBPK model of clonidine adequately predicted the PK of clonidine for all dosing regimens and routes of administration. We optimized our adult model using the adult development data sets (Table 2) by changing the parameters lipophilicity (log P) and fraction unbound. When we compared our optimized model with the development and independent evaluation data sets, the optimized model met our predetermined acceptance criteria (Figure 1; Table 4). We then compared our oral model predictions with the observed data from oral studies, and they met our predetermined acceptance criteria (Figure 2; Table 4). Our model slightly underestimated observed plasma concentrations after intravenous administration (Figure 1) and slightly overestimated observed plasma concentrations after oral administration (Figure 2).

Pediatric PBPK Model Prediction. The pediatric PBPK model was evaluated given data from Nielsen et

Figure 1. Adult optimized model. The physiologically based pharmacokinetic model concentration-time predictions of clonidine after intravenous injection doses of 275 µg (Panel A) and 3.36 µg/kg (Panel B). Solid black line represents the median predicted concentration; blue shaded area represents the 90% prediction interval; observed data from the adult development data sets[23,24] are represented by solid red squares.

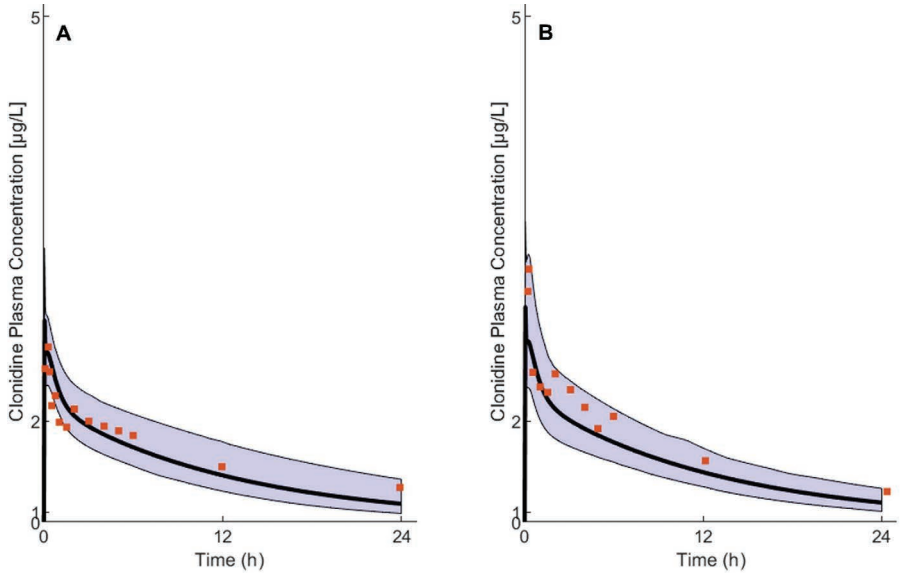

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Table 4. Average Fold Error (AFE) in Concentration for All Clonidine Adult PBPK Models

Study	N	Dose	AFE
Adult Development Data Sets			
Frisk-Holmberg[23]	13	275 µg IV bolus	0.82
Frisk-Holmberg[24]	21	3.36 µg/kg IV bolus	0.99
Adult Verification Data Sets			
Anavekar[26]	18	250 µg oral	1.06
Arndts[27]	7	75 µg oral	0.8
Wing[28]	5	300 µg oral	1.09

PBPK, physiologically based pharmacokinetic

al[30] and Larsson et al.[31] We observed good model predictability when comparing predicted and observed concentration-time data for both data sets, and they met our predetermined criteria (Figure 3; Table 5). The predictions were better with pediatric observed data set with intravenous administration (Nielsen et al[30]) compared with the data set with oral administration (Larsson et al[31]).

Dosing Simulations. The simulations showed that the C_{max} of clonidine after administration of current clinically used dosages of 6 µg/kg for NAS and NOWS, 0.1 mg/day, 0.15 mg/day, and 0.4 mg/day for Tourette's and ADHD did not achieve the C_{max} to match the optimal target clonidine concentration of 40.5 nM (9.3 ng/mL). As a result, the typically given doses of 6 µg/kg and 0.1 to 0.4mg/day are not sufficient for achieving maximum α-2 adrenergic agonist activity for treating Tourette's and ADHD. The exposure matching analysis using the simulations showed that the doses 30 µg/kg for neonates and 0.9 mg per day for ADHD and Tourette's population are optimal to reach the target concentration of α-2 adrenergic agonist activity. Table 6 provides the average C_{max} values of clonidine from simulations with various doses of clonidine in different pediatric age groups.

Discussion

In this study, we utilized the PBPK modeling approach to predict the PK of clonidine at various dosing regimens in the pediatric population across the age spectrum. The pediatric model was scaled from the adult model and was able to predict the pharmacokinetics of clonidine in children. The verified pediatric model was used to simulate the clonidine concentrations and identify the optimal clonidine dosing to achieve maximum central α-2 agonist activity that may result in better therapeutic efficacy to treat NAS, NOWS, ADHD, and Tourette's syndrome.[40] Currently, there are no guidelines on clonidine dosing in the pediatric population. Inaccurate clonidine dosing can result in serious adverse events such as hypotension, bradycardia, sedation, and somnolence.[41] In a recently reported incident, clonidine caused severe hypotension and sedation in a 5-year-old boy who accidentally overdosed.[42]

Although clonidine is widely used in pediatrics, there is limited understanding of its PK in this population. We are the first to report a pediatric PBPK model of clonidine that can provide dosing recommendations to treat NAS, ADHD, and Tourette's syndrome. Ke et al,[22] in 2013 reported a PBPK model of clonidine to

Figure 2. Adult verification model. The physiologically based pharmacokinetic model concentration-time predictions of clonidine after oral doses of 250 µg (Panel A), 75 µg (Panel B), and 300 µg (Panel C). Solid black line represents the median predicted concentrations: blue shaded area represents the 90% prediction interval; observed data from the adult verification data sets[26–28] are represented by solid red squares.

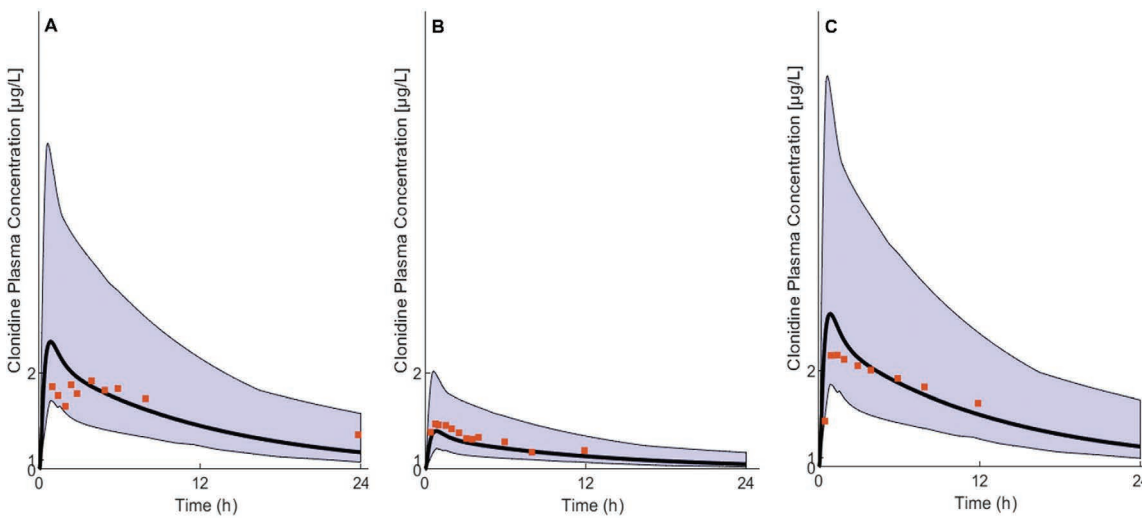

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Figure 3. Pediatric verification model. The physiologically based pharmacokinetic model concentration-time predictions of clonidine in pediatric population after intravenous bolus dose of 3 µg/kg (Panel A) and oral dose of 4 µg/kg (Panel B). Solid black line represents the median predicted concentrations; gray shaded area represents the 90% prediction interval; observed data from pediatric verification data sets[30,31] are represented by solid red squares.

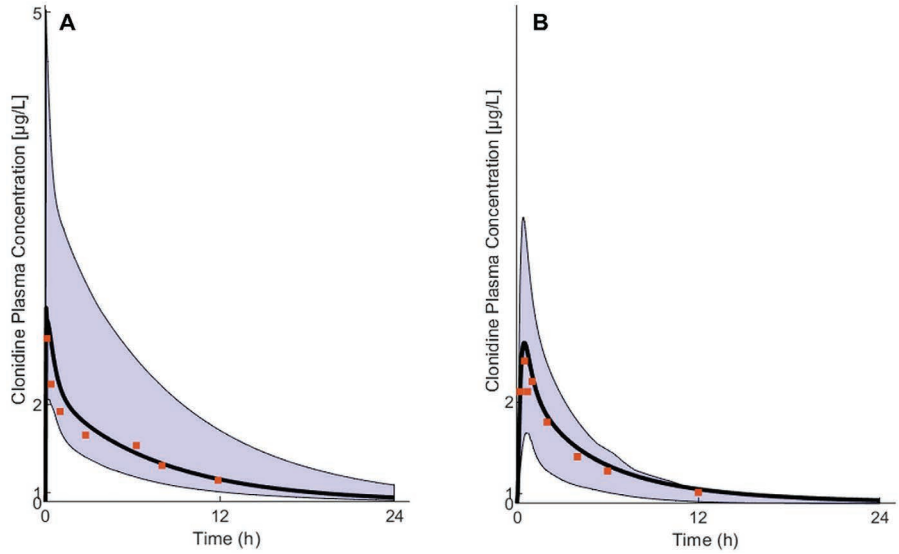

Table 5. Average Fold Error (AFE) in Concentration for All Clonidine Pediatric PBPK Models

S. No	Study	N	Dose	AFE
1	Nielsen[30]	21	3 µg/kg IV bolus	1.11
2	Larsson[31]	8	4 µg/kg oral	1.12

PBPK, physiologically based pharmacokinetic

Table 6. Simulated C_{max} of Clonidine Across Pediatric Ages at Various Doses

Population	Dose	Route	C_{max} (ng/mL)
Neonates	6 µg/kg	Oral	2.13
Neonates*	**30 µg/kg**	**Oral**	**10.87**
6 yr to 17 yr – typical ADHD and Tourette's pediatric population	0.1 mg/day	Oral	1.18
6 yr to 17 yr – typical ADHD and Tourette's pediatric population	0.4 mg/day	Oral	4.74
6 yr to 17 yr – typical ADHD and Tourette's pediatric population	**0.9 mg/day**	**Oral**	**9.94**

C_{max}, maximum plasma concentration

* The doses in bold are the optimal doses that reached a target C_{max} of 9.3 ng/mL based on α-2 agonist activity of clonidine.

predict its disposition in pregnant women. Their model incorporated the gestational age-dependent changes in maternal physiology and hepatic CYP2D6, CYP3A5, and CYP1A2 activity. We followed a similar approach for clonidine pediatric PBPK model development, wherein we incorporated age-related physiological changes and ontogeny of CYP2D6, CYP3A5, and CYP1A2 activity in pediatric populations at various age groups.[20] Similar to the Ke et al[22] model, our model can also be used in the future to evaluate the drug-drug interactions of clonidine with other drugs used in this population that may inhibit or induce CYP2D6, CYP3A5, and CYP1A2 activity.

The recommended optimal dose of clonidine based on our pediatric PBPK model simulations for neonates was 30 µg/kg and 0.9 mg/day for children (6–17 years age, commonly reported age group diagnosed with ADHD and Tourette's syndrome). The recommended optimal dose in neonates is 5.1 times higher than the currently used dose, whereas in children, the recommended dose is only 2.25 times higher than the currently used dose. This is expected as the ontogeny of CYP2D6 enzyme, which accounts for 67% of clonidine hepatic metabolism, shows a rapid increase during

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neonatal development, reaching adult levels within 28 days.[43] Furthermore, the higher magnitude of dose increase in neonates can also be explained by the excretion of clonidine by kidneys. There is a rapid increase of glomerular filtration rate in neonates, reaching about 50%–60% of the adult values and therefore resulting in a rapid elimination of clonidine in neonates.[44] Our PBPK model predictions show that in current clinical practice, clonidine may be underdosed in children to treat ADHD, Tourette's syndrome, NAS, and NOWS. After validating our model predictions with data from prospective clinical studies in children with ADHD, Tourette's syndrome, NAS, and NOWS, an increase in clonidine dose may be implemented in clinical practice to ensure adequate clonidine concentrations are reached for adequate α-2 agonist activity. The CYP enzymes CYP1A2, CYP3A4, and CYP2D6, responsible for the hepatic metabolism of clonidine, are undetectable during gestation, and therefore we do not expect any change in clonidine hepatic metabolism with gestational age.[45] However, it is well known that glomerular filtration rate (GFR) in neonates at birth increases with gestational age, and around 50% of clonidine is excreted by renal route, clonidine dosing must be reduced in preterm neonates to avoid any dose-related adverse events.[46] Based on the availability of clonidine PK data in preterm neonates, our pediatric clonidine PBPK model can be used to predict clonidine PK in preterm neonates and develop optimal dosing regimens in preterm neonates based on their gestational age.

Our clonidine pediatric PBPK model has some limitations. The first is that clonidine is often given in routes other than intravenous and oral, with two other common routes being nasal and transdermal administration. Our model can only accommodate intravenous and oral dosing regimens including oral suspension,. It does not currently extend to other routes of clonidine administration such as transdermal or nasal. There are limited to no clinical pharmacokinetic (PK) data available for those routes in children. However, in the future this PBPK model could easily be modified to accommodate clonidine dosing by other routes such as transdermal and nasal once the clinical PK data are available. The second limitation is that the target concentration of clonidine's central α-2 agonist activity used to decide optimal dosing was obtained from animal studies. A target concentration of clonidine with α-2 agonist activity derived from human experiments will be more appropriate. Finally, our PBPK model predictions must be verified with data from robust, prospective PK/PD studies of clonidine in children with ADHD, Tourette's, sedation, NAS, and NOWS before implementation in clinical practice.

Conclusion

In conclusion, the pediatric PBPK model of clonidine scaled from the adult PBPK model and verified using the pediatric PK data provides dosing recommendation for clonidine in different pediatric age groups. The model simulations showed that the current dosing regimen of clonidine used to treat NAS in neonates and ADHD and Tourette's syndrome in children did not adequately reach target concentrations to achieve maximal α-2 agonist activity. Based on pediatric PBPK model simulations, the doses 30 μg/kg for neonates and 0.4 mg/day for children are recommended to reach a target concentration that are predicted to result in maximal α-2 agonist activity. The pediatric PBPK model described in this study can be extended to other pediatric age groups and route of administration as needed and can also be used to evaluate the drug-drug interactions of clonidine with other medications used in these pediatric populations. However, the model predictions must be tested and confirmed with real-world clinical data to ensure they translate effectively to clinical practice.

Article Information

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References

1. Wood RA. The therapeutic uses of clonidine. *Scott Med J*. 1979;24(3):226–232.
2. Fitzgerald PJ. Elevated norepinephrine may be a unifying etiological factor in the abuse of a broad range of substances: alcohol, nicotine, marijuana, heroin, cocaine, and caffeine. *Subst Abuse*. 2013;7:171–183.

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3. Houston MC. Clonidine hydrochloride: review of pharmacologic and clinical aspects. *Prog Cardiovasc Dis*. 1981;23(5):337–350.
4. Tang F, Ng CM, Bada HS, Leggas M. Clinical pharmacology and dosing regimen optimization of neonatal opioid withdrawal syndrome treatments. *Clin Transl Sci*. 2021;14(4):1231–1249.
5. Newcorn JH, Krone B, Dittmann RW. Nonstimulant treatments for ADHD. *Child Adolesc Psychiatr Clin N Am*. 2022;31(3):417–435.
6. Hollis C, Pennant M, Cuenca J, et al. Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with Tourette syndrome: a systematic review and qualitative analysis. *Health Technol Assess*. 2016;20(4):1–450, vii–viii.
7. Leikin JB, Mackendrick WP, Maloney GE, et al. Use of clonidine in the prevention and management of neonatal abstinence syndrome. *Clin Toxicol (Phila)*. 2009;47(6):551–555.
8. Bromfalk A, Hultin M, Myrberg T, et al. Postoperative recovery in preschool-aged children: a secondary analysis of a randomized controlled trial comparing premedication with midazolam, clonidine, and dexmedetomidine. *Paediatr Anaesth*. 2023;33(11):962–972.
9. Connor DF, Fletcher KE, Swanson JM. A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1999;38(12):1551–1559.
10. Connor DF, Barkley RA, Davis HT. A pilot study of methylphenidate, clonidine, or the combination in ADHD comorbid with aggressive oppositional defiant or conduct disorder. *Clin Pediatr (Phila).* 2000;39(1):15–25.
11. Kubota T, Hirota K, Yoshida H, et al. Inhibitory effect of clonidine on ketamine-induced norepinephrine release from the medial prefrontal cortex in rats. *Br J Anaesth.* 1999;83(6):945–947.
12. Leckman JF, Hardin MT, Riddle MA, et al. Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry*. 1991;48(4):324–328.
13. Besag FM, Vasey MJ, Lao KS, et al. Pharmacological treatment for Tourette syndrome in children and adults: what is the quality of the evidence? A systematic review. *J Psychopharmacol*. 2021;35(9):1037–1061.
14. Bader MY, Zaghloul N, Repholz A, et al. A retrospective review following the addition of clonidine to a neonatal abstinence syndrome treatment algorithm. *Front Pediatr*. 2021;9:632836.
15. Keranen A, Nykanen S, Taskinen J. Pharmacokinetics and side-effects of clonidine. *Eur J Clin Pharmacol*. 1978;13(2):97–101.
16. Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia*. 1999;54(2):146–165.
17. Kern SE. Challenges in conducting clinical trials in children: approaches for improving performance. *Expert Rev Clin Pharmacol.* 2009;2(6):609–617.
18. Zhao P, Zhang L, Grillo JA, et al. Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin Pharmacol Ther*. 2011;89(2):259–267.
19. Yellepeddi V, Rower J, Liu X, et al. State-of-the-art review on physiologically based pharmacokinetic modeling in pediatric drug development. *Clin Pharmacokinet*. 2019;58(1):1–13.
20. Open Systems Pharmacology Suite Manual. Accessed July 31, 2023. https://www.open-systems-pharmacology.org/
21. Clonidine. Accessed July 31, 2023. https://go.drugbank.com/drugs/DB00575
22. Ke AB, Nallani SC, Zhao P, et al. A physiologically based pharmacokinetic model to predict disposition of CYP2D6 and CYP1A2 metabolized drugs in pregnant women. *Drug Metab Dispos*. 2013;41(4):801–813.
23. Frisk-Holmberg M, Edlund PO, Paalzow L. Pharmacokinetics of clonidine and its relation to the hypotensive effect in patients. *Br J Clin Pharmacol.* 1978;6(3):227–232.
24. Frisk-Holmberg M, Paalzow L, Edlund PO. Clonidine kinetics in man–evidence for dose dependency and changed pharmacokinetics during chronic therapy. *Br J Clin Pharmacol.* 1981;12(5):653–658.
25. Maharaj AR, Barrett JS, Edginton AN. A workflow example of PBPK modeling to support pediatric research and development: case study with lorazepam. *AAPS J*. 2013;15(2):455–464.
26. Anavekar SN, Jarrott B, Toscano M, Louis WJ. Pharmacokinetic and pharmacodynamic studies of oral clonidine in normotensive subjects. *Eur J Clin Pharmacol*. 1982;23(1):1–5.
27. Arndts D, Doevendans J, Kirsten R, Heintz B. New aspects of the pharmacokinetics and pharmacodynamics of clonidine in man. *Eur J Clin Pharmacol*. 1983;24(1):21–30.
28. Wing LM, Reid JL, Davies DS, et al. Pharmacokinetic and concentration-effect relationships of clonidine in essential hypertension. *Eur J Clin Pharmacol*. 1977;12(6):463–469.
29. PK Sim Ontogeny Database Version 7.3. Accessed August 14, 2023. https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/master/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf
30. Nielsen BN, Anderson BJ, Falcon L, et al. Pharmacokinetics of an intravenous bolus dose of clonidine in children undergoing surgery. *Paediatr Anaesth*. 2020;30(5):607–613.
31. Larsson P, Nordlinder A, Bergendahl HT, et al. Oral bioavailability of clonidine in children. *Paediatr Anaesth*. 2011;21(3):335–340.
32. Cutler AJ, Mattingly GW, Jain R, O'Neal W. Current and future nonstimulants in the treatment of pediatric ADHD: monoamine reuptake inhibitors, receptor modulators, and multimodal agents. *CNS Spectr.* 2022;27(2):199–207.
33. Mechler K, Banaschewski T, Hohmann S, Hage A. Evidence-based pharmacological treatment options for ADHD in children and adolescents. *Pharmacol Ther*. 2022;230:107940.
34. Joo SW, Kim HW. Treatment of children and adolescents with attention deficit hyperactivity disorder and/or Tourette's disorder with clonidine extended release. *Psychiatry Investig.* 2018;15(1):90–93.
35. Agthe AG, Kim GR, Mathias KB, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics*. 2009;123(5):e849–e856.
36. D'Abaco E. Does the addition of clonidine to opioid therapy improve outcomes in infants with neonatal

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abstinence syndrome? *J Paediatr Child Health*. 2021;57(1): 155–159.
37. Neuchat EE, Bocklud BE, Kingsley K, et al. The role of alpha-2 agonists for attention deficit hyperactivity disorder in children: a review. *Neurol Int*. 2023;15(2): 697–707.
38. Quezada J, Coffman KA. Current approaches and new developments in the pharmacological management of Tourette syndrome. *CNS Drugs*. 2018;32(1):33–45.
39. Gil DW, Cheevers CV, Kedzie KM, et al. Alpha-1-adrenergic receptor agonist activity of clinical alpha-adrenergic receptor agonists interferes with alpha-2-mediated analgesia. *Anesthesiology*. 2009;110(2):401–407.
40. Alojado ME, Ohta Y, Kemmotsu O. The effect of clonidine on the activity of neurons in the rat dorsal raphe nucleus in vitro. *Anesth Analg*. 1994;79(2):257–260.
41. Amneal Pharmaceuticals NY LLC. Clonidine hydrochloride - clonidine tablet, extended release. 2020 [rev. February 2020; cited April 2023]. In: DailyMed [Internet]. Bethesda, MD: National Library of Medicine (US); 2005. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=accb2879-7c0e-40d9-bc78-af78fc619609
42. Lindsay B. Watch, listen, and discover with Canada's public broadcaster. CBCnews, CBC/Radio Canada, March 16, 2023. https://www.cbc.ca/
43. van Groen BD, Nicolai J, Kuik AC, et al. Ontogeny of hepatic transporters and drug-metabolizing enzymes in humans and in nonclinical species. *Pharmacol Rev*. 2021;73(2):597–678.
44. Loebstein R, Koren G. Clinical pharmacology and therapeutic drug monitoring in neonates and children. *Pediatr Rev*.1998;19(12):423–428.
45. Fanni D, Ambu R, Gerosa C, et al. Cytochrome P450 genetic polymorphism in neonatal drug metabolism: role and practical consequences towards a new drug culture in neonatology. *Int J Immunopathol Pharmacol*. 2014;27(1):5–13.
46. Salem F, Johnson TN, Hodgkinson ABJ, et al. Does "birth" as an event impact maturation trajectory of renal clearance via glomerular filtration? Reexamining data in preterm and full-term neonates by avoiding the creatinine bias. *J Clin Pharmacol*. 2021;61(2):159–171.

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