JPPT | Letter to the Editor

Concern for Patient Harm Due to Potentially Supratherapeutic Clonidine Dosing Resulting From Physiologically Based Pharmacokinetic Modeling

To the Editor—We read with interest the recent publication by Yellepeddi et al[1] describing an innovative physiologically based pharmacokinetic (PBPK) model for predicting optimal clonidine doses for neonatal and pediatric indications. We agree with the authors' assertions regarding the dosing and pharmacokinetic challenges of using clonidine to effectively manage a variety of neonatal and pediatric disease states in which use has become common. Nonetheless, we have significant concerns that dosing up to 30 µg/kg/dose for neonates and 0.9 mg/day for older children and adolescents may cause patient harm if applied broadly.

As noted by the authors, excessive clonidine dosing may result in severe adverse drug events (ADEs), including hypotension, bradycardia, and somnolence; in younger age groups with unintentional ingestion, respiratory depression, and coma have been reported.[2–4] ADEs are thought to be dose related and have been observed in pediatric patients receiving labeled doses up to 0.4 mg/day.[5] Off-label use occurs frequently, potentially confounding ADE risk.

In neonates receiving clonidine for neonatal abstinence or neonatal opioid withdrawal syndromes, literature has consistently demonstrated the safety of doses up to 24 µg/kg/day divided every 3 to 6 hours, and up to 46% of these patients may be managed in the outpatient setting.[6,7] The PBPK model's proposal for single doses up to 30 µg/kg, roughly 500% of published dosing, has not been described in vivo. Investigators evaluating toxic clonidine ingestions have proposed 10 µg/kg or 0.1 mg as the dose thresholds at which patients younger than 4 years should receive medical evaluation.[2,3] Considering a mean term birthweight of 3.4 kg, most term neonates meet both thresholds at the PBPK model's proposed dose.[8] Additionally, while Yellepeddi et al[1] recommend the application of the PBPK model to develop clonidine dosing regimens for preterm neonates, modification to account for premature renal function at specific gestational ages was not further described. As gestational age of viability continues to decrease, the assumed rates of renal development included in the model become less reliable, requiring additional caution. Given that numerous studies have demonstrated the effectiveness of clonidine for neonatal abstinence and neonatal opioid withdrawal syndromes with standard dosing strategies, we question the utility of higher dosing and strongly support the authors' statement that prospective confirmation of safety and benefit resulting from higher dosing is imperative before such use becomes routine.

In older children and adolescents, defined within the PBPK model as 6 to 17 years of age, clonidine is prescribed for an array of psychiatric indications at a usual range of 0.1 to 0.4 mg/day.[1,4,9] Inconsistent benefit for some conditions validates the authors' assertion that dose escalation may be warranted, but established effectiveness for numerous indications challenges the suggestion that typical dosing is generally insufficient.[9] Current Centers for Disease Control and Prevention growth percentiles estimate a 20 kg mean weight for United States children at age 6. At this weight, 0.9 mg/day dosing corresponds to 15 to 23 µg/kg/dose divided 2 to 3 times daily. In a 2023 study of toxic clonidine ingestions in 70 patients aged 7 to 17 years, Duong et al[10] reported a median ingested dose of 13 µg/kg (IQR, 7–38). Bradycardia, hypotension, or altered mental status occurred in 91% of cases. At doses of only 5 to 10 µg/kg, moderate to severe bradycardia and hypotension occurred in 26% and 29% of patients, respectively, challenging the tolerability of PBPK-proposed doses.

The PBPK model represents an innovative approach to ontogenic pharmacokinetics and warrants further application to medications without established optimal dosing. Yellepeddi et al[1] acknowledge that extrapolating target clonidine concentrations from measurements of α-2 agonist activity in animal models is a limitation. If concentration-based activity proves similar in humans, we question whether maximal α-2 agonism is the appropriate target for symptom control rather than patient-specific, symptom-based approaches. We encourage judicious consideration of patient safety in the development of clinical trials evaluating higher clonidine-dosing strategies and emphasize that such research is necessary before applying the PBPK model to clinical practice.

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AUTHORS RESPONSE: Thank you for the opportunity to reply to the recent letter about our paper, "Optimal Dosing Recommendations of Clonidine in Pediatrics Using Physiologically Based Pharmacokinetic Modeling,"[1] which was published in *The Journal of Pediatric Pharmacology and Therapeutics*. We appreciate the authors' interest in our work and their efforts to raise awareness of the critical problem of clinical translation of model-based suggestions. We value the conversation regarding the possible clinical ramifications of our suggested modeling-based dosage strategies and recognize how crucial it is to guarantee patient safety. Below, each of the issues that were raised in the letter has been addressed.

1. Concern Regarding Potentially Supratherapeutic Clonidine Dosing and Adverse Drug Events

It is acknowledged that clonidine's adverse effects, including hypotension, bradycardia, and sedation, are dose-dependent and that pediatric patients may be particularly susceptible to these effects. However, we believe there may be a misconception regarding the intent of our study, as our article explicitly states that model-derived dosing recommendations must not be applied in clinical settings without validation through appropriate clinical data in the target population. The primary objective of the study was to demonstrate the utility of physiologically based pharmacokinetic (PBPK) modeling in characterizing clonidine pharmacokinetics across pediatric age groups, thereby providing insights that may guide future research and inform dose-optimization efforts. We stress that our model offers a platform for generating hypotheses rather than rapid practical application. We agree with your recommendation that caution must be exercised before adopting these doses widely and reiterate that our model provides a framework for guiding research rather than immediate clinical application implementing these doses.

2. Neonatal Dosing and Safety Considerations

We are aware that newborn opioid withdrawal syndrome and neonatal abstinence syndrome have been linked to clonidine dosages of up to 24 mcg/kg/day in recent research.[2,3] The 30 mcg/kg dose recommended for neonates in our paper was based on PBPK model simulations and resulted in plasma clonidine concentrations that are optimal for achieving target plasma concentrations for maximal α-2 adrenergic activity. This recommendation was not intended to be a "single" dose for administration in neonates. We want to clarify that our simulations were not used to establish a strict dosing schedule but rather to forecast exposure matching.

Regarding the safety threshold for medical evaluation at 10 mcg/kg or 0.1 mg,[4] we agree that caution is warranted. As we indicated in the discussion section, the availability of clonidine pharmacokinetic data in preterm newborns is necessary to guarantee the accuracy of model predictions when using our PBPK model for these patients. In the discussion section, we also stated that, depending on the gestational age of the preterm neonates, our PBPK model can be extrapolated to them. However, we did not go into greater detail about how to extrapolate our model to preterm infants because that was outside the purview of the manuscript.

3. Older Children and Adolescents: Risk of Toxicity

The authors of the letter have valid concerns about the 0.9 mg/day dose in older children and adolescents. Current dose recommendations range from 0.1 to 0.4 mg/day[5] as mentioned in their letter. Our model, however, showed that these dosages might not produce the desired α-2 adrenergic activity needed for the best possible treatment outcomes for Tourette's syndrome and attention-deficit/hyperactivity disorder. We appreciate the reference to Duong et al,[6] which highlights the risk of bradycardia and hypotension at doses as low as 5 to 10 mcg/kg. However, the findings given may not be applicable to a more controlled dosing of clonidine for therapeutic purposes because it came from acute clonidine poisoning caused by children accidentally consuming large quantities of clonidine. Our findings suggest that dose-optimization studies are warranted, but we emphasize in our manuscript that such recommendations must be verified through rigorous clinical studies before implementation.

4. Extrapolation From Animal Studies and Clinical Relevance of Target Concentration

Our selection of 40.5 nM as the plasma target concentration was derived from animal models,[7] and it has not yet been established if it can be directly applied to pediatric patients. Nevertheless, using PBPK modeling to define exposure-response relationships is a well-established approach in pediatric pharmacology.[8,9] Our results provide an initial estimate that should be validated through exposure-response studies in clinical settings. We concur that in dose-optimization trials, a symptom-based strategy is still essential.

5. Clinical Implementation and Need for Prospective Trials

We completely concur with the authors' concerns and reiterate the fundamental principle that model-based predictions need thorough verification before clinical implementation, even though they are useful for developing hypotheses and designing studies. Our manuscript makes it very evident that the PBPK model is not a final clinical recommendation but rather an evidence-based basis for additional research and not a definitive clinical guideline. Before applying model predictions, real-world verification through prospective pharmacokinetic or pharmacodynamic investigations is crucial, as mentioned in previous PBPK-based pediatric dose-optimization studies.[10–12]

Conclusion

We appreciate this conversation as a chance to emphasize how crucial it is to understand model-based results carefully and validate them appropriately in pediatric pharmacotherapy. Thank you for the authors' engagement, and we look forward to continued dialogue on the responsible application of pharmacokinetic modeling and more discussions about the appropriate use of pharmacokinetic modeling in clinical judgment.

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