

PBPK modelling-based estimation of safe and effective Molnupiravir doses for pediatric subpopulations against SARS-CoV-2

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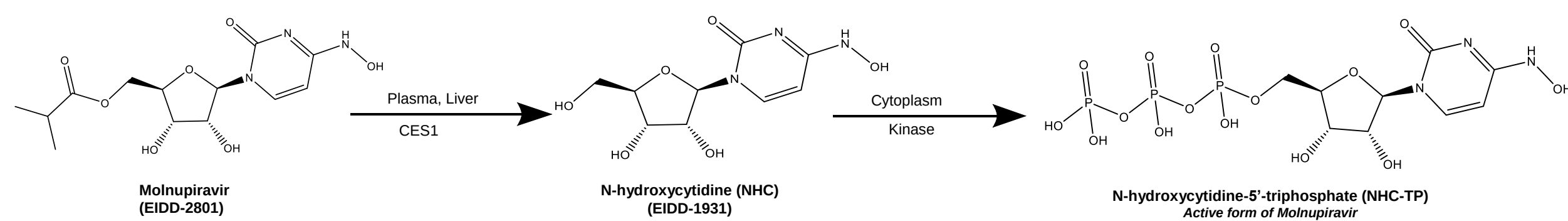
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Introduction

- Although COVID-19 pandemic has ended, SARS-CoV-2 will remain demanding therapeutic approaches for vulnerable subpopulations such as pediatrics [1].
- Molnupiravir, as an oral drug, can be a preferable option as compared to other approved drugs such as Remdesivir, Paxlovid® which presents challenges of intravenous administration requirement and drug-drug interaction potential respectively [2,3].
- Molnupiravir (EIDD-2801) is an orally active prodrug of ribonucleoside analog β-D-N4-hydroxycytidine (NHC; EIDD-1931), received emergency use authorization for treatment of COVID-19 by MHRA, US FDA in 2021 [4].
- Along with SARS-CoV-2, Molnupiravir has been found effective against a wide range of viruses including Ebola virus, Influenza, Venezuelan equine encephalitis virus, chikungunya virus, respiratory syncytial virus, hepatitis C virus, norovirus, and other coronaviruses [5].

Objective

- Estimate safe and effective doses of Molnupiravir in different pediatric age groups by employing carboxylesterase 1 (CES1) ontogeny based pediatric Molnupiravir-NHC PBPK model, while considering for bone toxicity potential of effective doses.



Conversion pathway of Molnupiravir into its active form through NHC.

Methodology

- Whole body PBPK model was developed by using PK-Sim® (v 11.2) (Open Systems Pharmacology) by middle out approach through training data set; followed by model qualification at different dose⁵.
- The esterase clearance (plasma, liver microsomes) parameters were also calculated by *in-vitro* stability study.
- CES1 based clearance (plasma, liver) was considered in model by incorporating extra compartment, enzyme $t_{1/2}$ [6] and reference abundance [7], while NHC clearance was considered as total hepatic clearance.
- Developed model was extrapolated to higher single (50-1600mg) and multiple doses (50mg-800mg) [4] and verified by visual comparison and ratios of C_{max} , Area under curve ($AUC_{0-\infty}$) of predicted to observed time concentration-time profiles in the range of 0.5 to 2.
- Pediatric models for Neonates (0-27 days), Infants (28 days -1 year), Early childhood (1-12 years) age groups were developed by extrapolating verified adult model by integrating CES1 ontogeny and age dependent physiological parameters.
- The models were developed from 5 to 75 mg/Kg B.I.D. for 5.5 days to achieve expose time above EC_{50} (0.67 for Omicron variant) [8] similar to adult recommended dose of 800 mg BID, While reference adult effective plasma exposure time above EC_{50} was calculated from validated adult 800 mg BID model.
- Maximal safe concentration to prevent bone toxicity in pediatric patients was allometrically derived from dogs bone toxicity study (safe dose level of 50 mg/Kg/day).

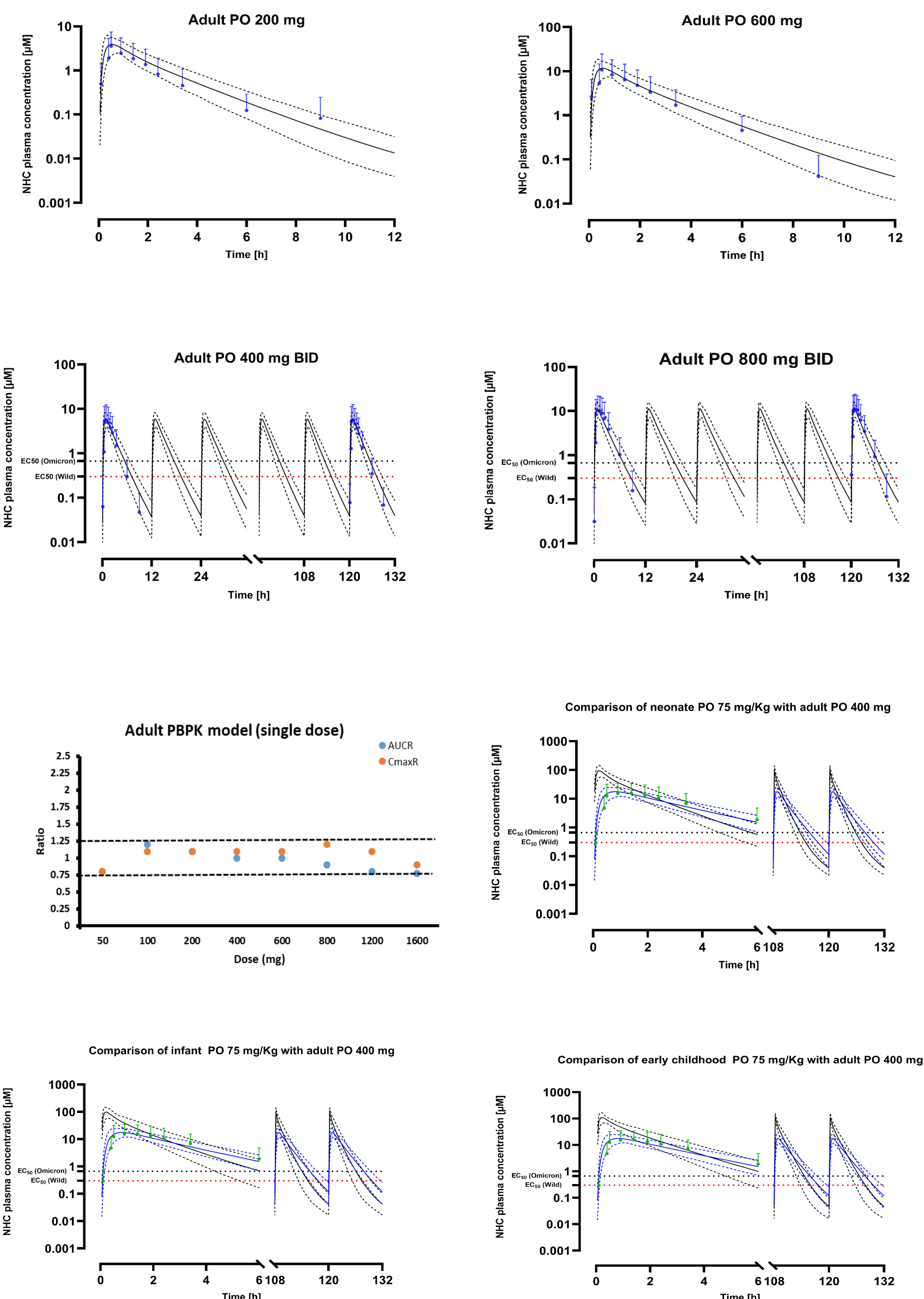
Drug-dependent parameters for Molnupiravir-NHC model

Properties	Molnupiravir	NHC	Reference
MW (g/mol)	329.31	259.22	4
LogP	0.46	0.10*	4, Shake flask
Plasma protein binding (%)	38.08	38.84	RED device®
Blood/Plasma ratio	0.48	0.45	PK-Sim
pKa	2.2, 10.2, 12.0	12.30*	4, Percepta ®
Solubility (mg/ml)	39.7	21	4
Hepatic clearance (CES1) (1/min)	15.13*	-	In-house
Plasma clearance (CES1) (1/min)	325.26*	-	In-house
Unspecified hepatic clearance (1/min)	-	2.36*	In-house
Specific intestinal permeability (cm/min)	0.000186**	-	PAMPA
Partition coefficient	PK-Sim standard		
Cellular permeability	PK-Sim standard		
Dissolution time, t1/2 (min)	10*	-	PK-Sim (Weibull)
Dissolution shape	0.59*	-	PK-Sim (Weibull)
GFR Ratio	1		

* Optimized values

Results

- Oral PBPK model successfully predicted Plasma NHC levels from 50 to 1600mg doses in single dose study, 50-800 mg BID multiple dose studies.
- Allometric scaling of Bone toxicity study in Dogs predicted highest possible safe dose of 27.8 mg/Kg/day i.e. 14 mg/kg BID for humans.
- The exposure time above EC_{50} for neonate, infant, early childhood models at maximum 75 mg/Kg BID dose were 7, 7.3, 7.9 hours respectively. However, pediatric models were not able to achieve $t_{>EC_{50}}$ similar to adult recommended dose of 800 mg BID i.e. 8.7 hours.
- The comparative study of plasma concentration time profile predictions of adult 1200 mg BID, a dose above the safe limit and recommended dose with pediatric 75 mg/Kg BID clearly indicates the multiple fold higher C_{max} values in all the pediatrics models with plasma concentration higher than 1200 mg dose in adults for 2.5, 2.75, 4 hours for neonates, infants, early childhood models respectively.



Conclusion

- Molnupiravir-NHC PBPK model successfully predicted PK for adult population.
- Pediatric PBPK models for different age groups suggest that effective plasma concentrations is infeasible for Molnupiravir in pediatric population within the safe dose limit.
- Ongoing efforts to link adult Molnupiravir model with pharmacodynamics (PD) effects to build PBPK/PD model to study dose-response relationship.

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