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IDENTIFICATION OF AGE-APPROPRIATE DOSING STRATEGIES OF BICTEGRAVIR IN NEONATES

Fazila Bunglawala[1], Rajith Rajoli[1], Alice Howarth[1], Hannah Kinvig[1], Nicolas Cottura[1], Andrew Owen[1], Marco Siccardi[1]
1- Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK
f.bunglawala@liverpool.ac.uk

OBJECTIVE

- To model the pharmacokinetics (PK) of bictegravir (BIC) in neonates and identify an age-appropriate dosing regimen.

BACKGROUND

- Physiologically-based PK (PBPK) modelling can be employed in early drug development to help inform selection of appropriate medicines at doses appropriate for vulnerable populations of patients including neonates.
- BIC is a HIV-1 integrase inhibitor that elicits a potent virological response [1] and has potential for treatment and prophylaxis within neonatal populations.
- Safety and PK of BIC have previously been reported in paediatric patients older than 6 years and adolescents.
- Dose optimisation in neonatal patients is complex and in the absence of empirical data, PBPK modelling may help inform knowledge gaps and dose selection.

METHODS

- The PBPK model was designed in Simbiology (MATLAB R2018a), incorporating neonatal maturation characteristics and mathematical descriptions of physiological and anatomical growth.
- Healthy virtual patients between 0 – 28 days were simulated.
- As BIC is predominantly metabolised by UGT1A1 and CYP3A4, the PBPK model was validated using physicochemical data from the surrogate substrates: raltegravir (RAL) (UGT1A1) and midazolam (MDZ) (CYP3A4).
- Experimental *in vitro* data for BIC was integrated into the model to aid prediction of BIC PK in the neonatal population.
- Additionally, BIC adult clinical data [2] were used for the validation of the PBPK model.
- Clearance in neonates was estimated via retrograde modelling from adult *in vivo* systemic clearance due to limited *in vitro* data.
- The PBPK model was evaluated by calculating the absolute average fold error (AAFE) and root mean squared error (RMSE) where appropriate.
- AAFE is a useful parameter to assess over or under-prediction of the model, values closer to 1 indicate a closer similarity with observed values.
- RMSE calculates the error between the predicted value and the observed value. RMSE is particularly sensitive to outliers and values closer to zero indicate a reliable prediction.
- The model was assumed to be qualified if the simulated values were within 2-fold of the mean reported values, AAFE were <2 and RMSE were <1 as per convention for the approach.

RESULTS

- For model verification, RAL PK data were split into two distinct age ranges: 1-7 days and 8-28 days. The dose for neonates in the first week of life is 1.5 mg/kg once daily (QD), increasing to 3 mg/kg twice daily (BID) from 2-4 weeks [3]. 100 healthy neonates were simulated and the model was adjusted accordingly. AAFE and RMSE values were within the verification criteria. *(Table 1)*
- Pre-existing clinical PK data for MDZ involved administration of an intravenous bolus of 0.2 $mg.kg^{-1}$ in neonates [4]. AAFE was calculated for each PK parameter. The model was deemed qualified as all values were within 1.5-fold of observed data *(Table 2)*, in agreement with accepted norms.

Table 1 AAFE and RMSE values from RAL validation

RAL PK Profile Verification	RAL 1.5 mg/kg Day 1-7	RAL 3.0 mg/kg Day 8- 28
AAFE	**1.25**	**1.39**
RMSE	**0.43**	**0.43**

Table 2 AAFE values from MDZ validation

MDZ Verification	Clinical	Simulated	AAFE
AUC (mg.h/L)	2.20	2.89	**1.314**
Cmax (mg/L)	0.41	0.42	**1.022**
C_{trough} (mg/L)	0.11	0.11	**1.020**
$CL_{systemic}$ (L/h)	0.41	0.38	**1.063**

- Verification of BIC in adults is summarised in Table 3. BIC multiple dose strategies were simulated in 100 healthy neonates with the aim of achieving plasma exposure comparable to therapeutic levels observed in adult patients **(C_{trough}: 2.61 mg/L and AUC_{24}: 102 mg*h/L)**. The PK parameters for each regimen are listed in Table 4. Regimens 2, 3, 5 & 6 predicted PK parameters comparable to those in adult patients *(Figure 1)*.

Table 3 AAFE values from BIC validation in adults

BIC Adult Verification (50 mg QD)	Clinical Geometric Mean (%CV)	Simulated Mean (%CV)	AAFE
AUC (mg.h/L)	102 (26.9)	110 (25.6)	**1.075**
C_{max} (mg/L)	6.15 (22.9)	6.21 (18.7)	**1.010**
C_{trough} (mg/L)	2.61 (35.2)	3.05 (36.7)	**1.167**
$CL_{systemic}$ (L/h)	0.54	0.61 (24.6)	**1.129**

Table 4 PK parameters of BIC multiple dose regimens 1-6.

BIC PK Parameters in Neonates							
Regimen	Total Dose (mg)	C_{max}[1] (mg/L)	AUC_{av} (mg.h/L)	C_{max}[2] (mg/L)	AUC (mg.h/L)	C_{trough} (mg/L)	T ½ (h)
1	Day 1-13 5mg Q48H; Day 14-28 5mg QD	2.53	42.18	2.06	37.00	1.47	43.0
2	Day 1-13 5mg Q48H; Day 14-28 7.5mg QD	3.34	50.32	2.91	59.09	2.09	44.2
3	Day 1-13 5mg Q48H; Day 14-28 10mg QD	3.90	54.00	3.37	67.50	2.38	40.2
4	Day 1-28 5mg QD	4.03	60.37	1.94	38.24	1.36	44.1
5	Day 1-19 5mg QD; Day 20-28 7.5mg QD	3.86	61.19	2.67	52.78	1.86	41.6
6	Day 1-19 5mg QD; Day 20-28 10mg QD	4.04	67.34	3.49	71.65	2.48	44.6

Cmax[1], Maximum plasma concentration over 28 day simulations; Cmax[2], Maximum plasma concentration after final dose has been administered; AUC_{av}, Average area under curve over 28 day simulations; AUC, Area under curve after final dose; C_{trough}, Minimum plasma concentration after final dose; T ½, half-life.

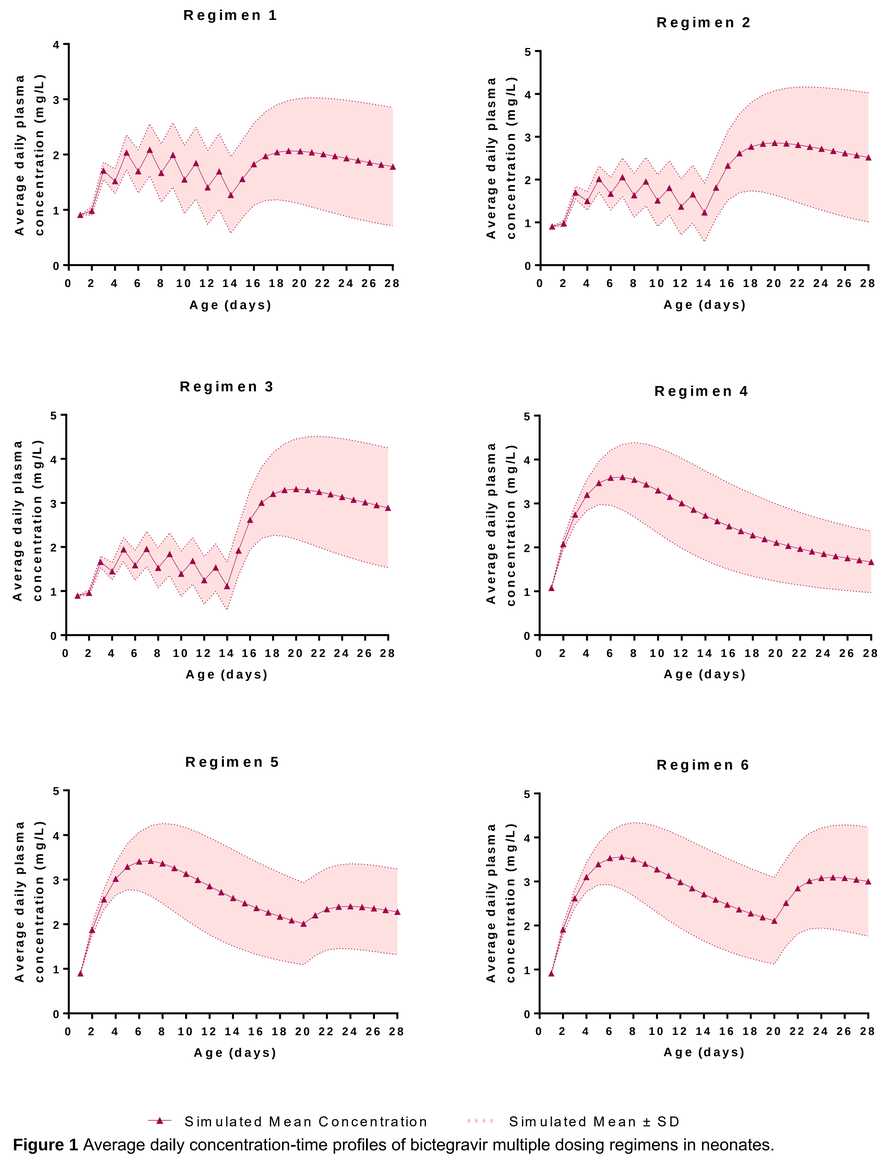

Figure 1 Average daily concentration-time profiles of bictegravir multiple dosing regimens in neonates.

CONCLUSION

- Following a thorough verification process, simulated data were in good agreement with observed clinical data (< 2 fold); our simulations suggest starting neonates on a 5 mg once daily dose, increasing to 7.5-10 mg after 2/3 weeks.
- Despite passing qualification criteria, the model is based on multiple assumptions including, but not limited to, transporter activity and tissue composition.

REFERENCES

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