

How modelling & simulation supported the drug development in children for a drug S



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Introduction

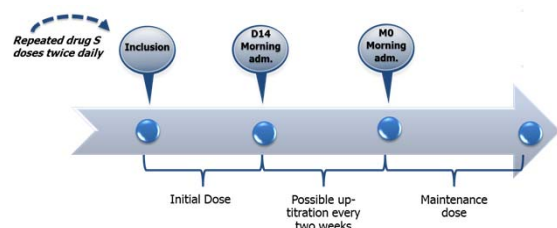
A clinical study was conducted in paediatric patient population treated with drug S (already marketed in adult) administered twice daily during one year. 70 patients were distributed as followed: 9 infants in age-subset [6-12[months (class1), 23 infants and children in age-subset [1-3[years (class 2), 26 children and adolescents in age-subset [3-18[years with weight <40 kg (class 3), 12 children and adolescents in age-subset [3-18[years with weight ≥ 40 kg (class 4). The drug S is 80 % metabolized via CYP3A4 and for about 20 % renally eliminated by glomerular renal filtration (GFR).

Objectives

The objectives of this study were to describe the PK of drug S and its active metabolite in this population, to assess potential differences in PK between age classes, and to assess whether the blood/plasma ratio and the PK/PD relationship are preserved between paediatric and adult populations.

Methods

Study design



Data

- 6 PK data were obtained at steady state after 5 blood sampling using dried blood spot and one plasma sample in order to assess the relationship between blood and plasma concentration. PK measurements were available for 70 patients.
- PD measurements were performed systematically just before each PK sampling.

Population PK analysis

- The relationship between blood concentration using DBS samples and plasma concentration was described through linear population models, for each analyte.
- To describe drug S and its metabolite blood concentrations in children, a joint population PK model was developed taking into account weight (with weight effects fixed to the allometric values of 0.75 and 1 on clearances and volumes of distribution, respectively [1]) & age effects through maturation functions [2].

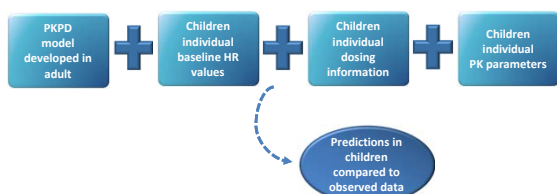
Model Assumptions

Parameter	Justification	Assumption
Drug S bioavailability	Cannot be estimated after oral administration	Fixed to adult value
Metabolite absorption rate constant	Design too sparse	Fixed to adult value
First pass effect fraction	Cannot be estimated with only oral administration of the parent drug	Fixed to adult value
Metabolite distribution volume	Not identifiable	Equal to drug S distribution volume

- Model-building was guided by MONOLIX's BIC and was evaluated using goodness-of-fit plots and NPDE.

- Plasma PK exposure parameters were calculated in children using converted plasma PK profiles.

Application of the adult PK/PD model to paediatric data



Results

Final children PK model

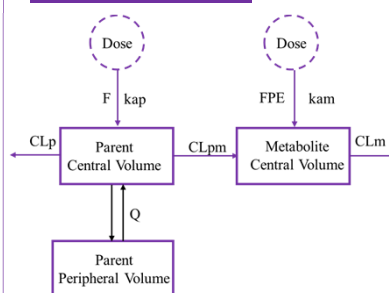


Fig.1: Final PK model

k_{ap} : drug S first-order absorption rate constant,
 F : drug S bioavailability,
 k_{am} : absorption rate constant of the metabolite,
 FPE : first pass effect fraction,
 V_c : volume of central compartment,
 V_p : volume of peripheral compartment,
 CL_{pm} : metabolite formation clearance,
 CL_p : drug S other elimination pathway clearance,
 CL_m : metabolite elimination clearance

Parameter (unit)	Estimate (RSE %)	IIV(%) (RSE %)	IOV(%) (RSE %)
k_{ap} (1/h)	2.14 (28)	168 (15)	-
F	0.38 fixed	60.3 (9)	64.9 (13)
k_{am} (1/h)	0.51 fixed	-	-
FPE	0.18 fixed	-	-
V_c (L)	24.9 (10)	18.7 (65)	-
V_p (L)	82.6 (11)	54.7 (20)	-
Q (L/h)	1.85 (19)	93.9 (20)	-
CL_{pm} (L/h)	9.21 (8)	14.2 (55)	-
CL_p (L/h)	1.02 (17)	27.4 (50)	-
CL_m (L/h)	48.6 (6)	22.9 (17)	-
σS prop (%)	38.9 (7)	-	-
σM add (ng/mL)	0.122 (17)	-	-
σM prop (%)	17.7 (15)	-	-

Table 1: Final population pharmacokinetic parameters; IIV : inter-individual variability, IOV : inter-occasion variability, RSE : relative standard error.

Model evaluation : No bias in predictions

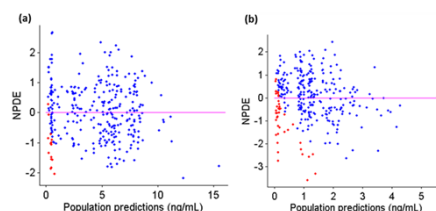


Figure2 : Drug S (a) and its metabolite (b) Normalized Prediction Distribution Error (NPDE) versus population predictions (ng/mL). Blue dots for concentrations above the quantification limit. Red dots for concentrations below the quantification limit.

Plasma PK exposure parameters: Higher dose/kg necessary in younger children

	Age class				
		[6-12[months	[1-3[years	[3-18[years WT < 40 kg	[3-18[years WT ≥ 40 kg
Drug S	AUC _{24,ss} (h.ng/mL/kg)	16	8.0	7.2	3.6
	C _{max} (ng/mL/kg)	2.1	1.6	0.9	0.41
	AUC _{24,ss} (h.ng/mL/kg)	3.7	2.3	2.1	1.1
Metabolite	C _{max} (ng/mL/kg)	0.31	0.27	0.16	0.0033

Adult PK/PD relationship conserved in children

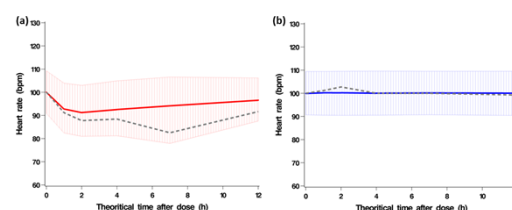


Figure3: Predicted corrected VPC (pcVPC) for heart rate (bpm) following drug S (a) or placebo (b) treatment.

Conclusions

This work underlines the importance of modelling and simulations for the analysis of clinical studies for drug development in pediatric populations. The assessment of PK and PK/PD relationship in children through the use of integrated analysis tools allowed to draw conclusions regarding the effects of drug S in children.

References:

- Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36.
- Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet. 2006;45(9):931-56.