PBPK model-based extrapolation from adults to children to predict furosemide oral solution bioavailability

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INTRODUCTION

Furosemide is a loop diuretic that has been used in adults and children for decades, mainly for the treatment of heart failure, arterial hypertension and other pathologies that require reducing cardiac preload [1,2]. In paediatrics, furosemide is recognized as one of the most effective diuretics in clinical practice [3]. Information of the oral absorption of furosemide in the paediatric population is scarce and there is no predictive models available that allow describing absorption and bioavailability of the drug in oral formulations intended for use in paediatrics, such as oral solutions (OS) and orodispersible tablets (ODT).

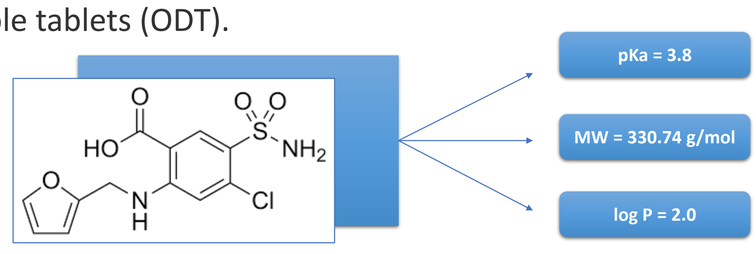

Figure 1. Furosemide molecular structure and basic Chemical information.

OBJECTIVES, MATERIALS AND METHODS

- The aim of this work was to develop a physiologically based pharmacokinetic (PBPK) model that allows predicting the bioavailability of an oral solution of furosemide in different age groups within the paediatric population.
- A paediatic PBPK (P-PBPK) model was developed using PK-Sim® (Open Systems Pharmacology) software [4]. A previously published PBPK model of furosemide in adults [5] was used as a starting point and adequately scaled to paediatric population considering the demographic and physiological characteristics of the different age subgroups.
- The model was qualified using pharmacokinetic data following intravenous (IV) and oral administration of furosemide from scientific literature [6,7].
- A prediction of AUC and/or Cmax with a relative bias of less than 30% was established as acceptance criteria.
- Simulations of AUC for 5 paediatric age ranges after iv and oral solution administration were performed to estimate the corresponding oral bioavailability.

RESULTS AND DISCUSSION

Table 1. Drug-dependent and physiology-dependent parameters of the furosemide PBPK model (absorption, metabolism and excretion sections). For the values extracted from scientific literature, the corresponding reference is indicated and in the case of parameter optimization it is abbreviated as PO.

Parameter [Reference]	Mean value (range)	Unit	Description
GFR fraction [5]	1.00	-	Fraction of filtered drug in the urine
UGT1A9 Km [5]	72.0	µmol/L	UGT1A9 Michaelis-Menten constant
UGT1A9 kcat [5]	954.3	1/min	UGT1A9 catalytic rate constant
MRP4 Km [5,8]	28.0	µmol/L	MRP4 Michaelis-Menten constant
MRP4 kcat [5,8]	6841.1	1/min	MRP4 transport rate constant
OAT3 Km [8]	21.5	µmol/L	OAT3 Michaelis-Menten constant
OAT3 kcat [5, PO]	8226.8	1/min	OAT3 transport rate constant
OAT1 Km [8, PO]	38.9	µmol/L	OAT1 Michaelis-Menten constant
Duodenum ESA adults [PKSim®, 9]	294 (276-308)	cm^2	Effective surface area for adults 21-52 years
Kidney specific GFR adults [PKSim®, 9]	23.79 (22.62-24.91)	mL/min/100g	Specific glomerular filtration rate for adults
Fasting GET adults [PKSim®, 9]	15.0 (6.2-42.5)	min	Gastric emptying time
Duodenum [PKSim®, 10] ESA neonate [PKSim®, 10]	260 (252-271)	cm^2	Effective surface area for neonates (0 years)
Kidney specific GFR neonate [PKSim®, 10]	10.31 (9.71-10.72)	mL/min/100g	Specific glomerular filtration rate for neonate (0 years)
Fasting GET neonate [PKSim®, 10]	12.0 (5.0-55.5)	min	Gastric emptying time

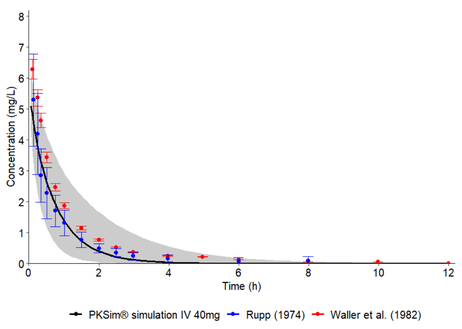

Figure 2. Simulated plasma concentrations versus time (black color) with corresponding 95%CI (grey color) for a population of n=500 healthy adults aged 21 to 52 years following 40 mg IV administration of furosemide.

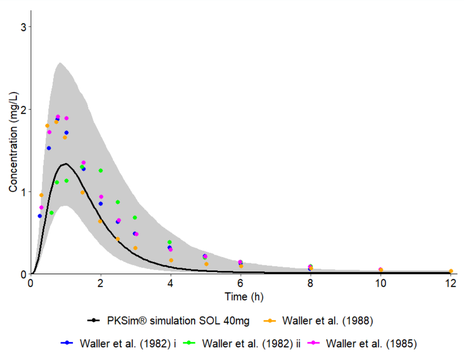

Figure 3. Simulated plasma concentrations versus time (black color) with its corresponding 95%CI (grey color) for a population of n=500 healthy adults aged between 20 and 52 years following the administration of 40mg of furosemide as an oral solution.

Table 2. Mean parameters and 95% CI or biological and physiological variables generated in virtual populations (n=500) using the scaling function of the software, according to the different age ranges used in this work.

Parameter and unit	Median and range					
	Neonate	1 month – <2 years	≥2 – <6 years	≥6 – <12 years	≥12 – <18 years	Adults
Weight (kg)	3.3 (2.6 - 4.0)	10.0 (4.0 – 18.0)	18.0 (9.1 – 30.2)	30.5 (18.5 – 49.5)	50.0 (28.5 – 82.0)	66.0 (45.0 – 82.5)
Height (cm)	50.0 (45.3 – 58.0)	77.5 (52.5 – 92.5)	102.5 (80.5 – 124.0)	127.5 (105.0 – 160.5)	150.5 (130.0 – 188.8)	166.6 (140.1 – 198.5)
Fasting gastric emptying time (min)	17.5 (7.5 – 60.0)	16.0 (5.5 – 60.0)	16.0 (4.8 – 52.5)	15.5 (5.2 – 53.5)	15.0 (5.0 – 55.5)	16.3 (5.0 – 60.0)
Mean salivary volume (mL)	0.27 (0.21 – 0.35)	0.80 (0.27 – 1.40)	1.40 (0.80 – 2.60)	2.75 (1.55 – 4.10)	4.00 (2.40 – 6.25)	4.90 (3.35 – 6.70)
Duodenum effective surface area factor	2.66 (2.53 – 2.79)	2.68 (2.54 – 2.80)	2.69 (2.54 – 2.79)	2.79 (2.65 – 2.94)	2.93 (2.78 – 3.07)	2.94 (2.77 – 3.08)
Stomach length (cm)	6.1 (5.8 – 6.3)	8.2 (6.2 – 10.4)	11.8 (9.6 – 14.9)	14.8 (13.0 – 17.5)	18.7 (16.4 – 19.6)	19.5 (19.3 – 20.8)
Stomach volume (mL)	7.5 (5.0 – 13.5)	22.5 (7.5 – 40.5)	43.0 (21.5 – 88.5)	82.5 (50.5 – 140.5)	135.5 (70.0 – 200.0)	160.5 (90.0 – 242.5)

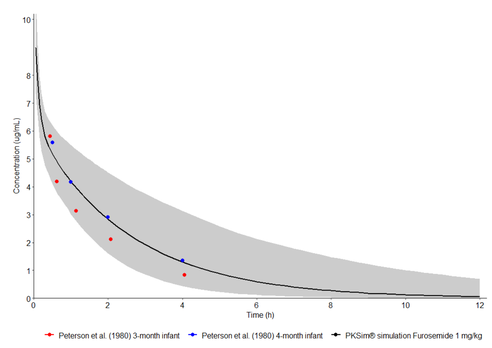

Figure 4. Population adjustment n=500 for plasma concentrations of furosemide after administration of 1 mg/kg intravenously in infants.

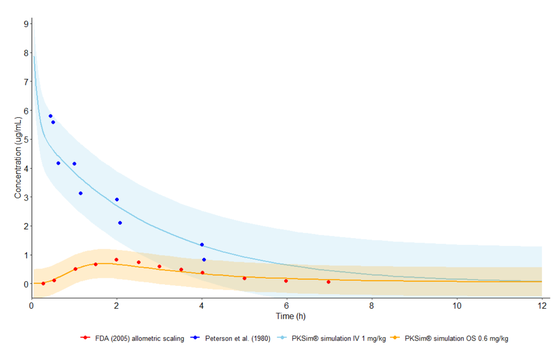

Figure 5. Visual Predictive Check (VPC) n=500 for simulated furosemide plasma concentrations after 1mg/kg IV and 0.6mg/kg OS administration in infants.

Table 3. Prediction by age group of pharmacokinetic metrics for intravenous (IV) and oral solution (OS) administration of 0.6 mg/kg furosemide. C_0 refers to the initial concentration (t=0) and C_{max} to the maximum concentration observed.

Formulation	Parameter (unit)	Neonate	1 month – <2 years	≥2 – <6 years	≥6 – <12 years	≥12 – <18 years	Adults
IV	$AUC_{0\text{-}inf}$ (mg.h/L)	8.94 (4.89 – 16.41)	10.14 (5.60 – 21.20)	9.73 (5.51 – 19.45)	10.29 (5.95 – 21.90)	4.03 (2.29 – 8.46)	4.08 (2.48 – 8.60)
IV	C_0 (mg/L)	4.85 (4.32 – 5.44)	5.39 (4.40 – 6.58)	5.35 (4.87 – 6.01)	5.58 (5.07 – 6.18)	5.61 (4.97 – 6.30)	5.63 (4.24 – 7.22)
OS	$AUC_{0\text{-}inf}$ (mg.h/L)	6.09 (3.18 – 11.04)	6.73 (3.11 – 14.85)	6.13 (2.96 – 11.88)	6.43 (3.18 – 13.16)	2.40 (0.98 – 4.51)	3.02 (0.80-6.78)
OS	C_{max} (mg/L)	0.86 (0.33 – 1.66)	0.74 (0.23 – 1.73)	0.64 (0.23 – 1.45)	0.61 (0.22 – 1.52)	0.36 (0.14 – 0.88)	1.45 (0.52-2.63)
OS	F	0.68 (0.64 – 0.72)	0.66 (0.62 – 0.70)	0.63 (0.60 – 0.66)	0.63 (0.60 – 0.65)	0.60 (0.57 – 0.64)	0.63 (0.61 – 0.68)

- A prediction of AUC and/or Cmax with a relative bias of less than 30% was established as acceptance criteria.
- P-PBPK model adequately scaled allows predicting the pharmacokinetics of furosemide in paediatrics, obtaining AUC values with a relative error of less than 20% compared to literature data [7,11,12].
- In all cases, mean bioavailability did not deviate significantly from previously reported values for adults of approximately 0.64 and 0.60 for furosemide oral solution and tablets, respectively [8,9].
- A small increase in OS bioavailability was observed in the youngest age groups, however it is not considered relevant due to the high variability of the metric [8,10,12].

CONCLUSIONS

- The developed PBPK model can be considered as an acceptable alternative tool to evaluate potential age dependencies on the bioavailability of a paediatric oral formulation of furosemide. Based on the PBPK model-based predictions, no significant differences in the bioavailability of furosemide are expected between adults and paediatric population.
- Even if a small increase in the bioavailability of the oral solution was observed in the lower age subgroups compared to adults (geometric mean ratio percentage difference was lower than 8.0%), this was not considered relevant taking into account the high variability of the metric reported in the literature (range from 10% to 90%) for adults [13,14,15,16,17].

REFERENCES

All the bibliographical references consulted in this work can be viewed through the following QR code: