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European Paediatric Translational Research Infrastructure

In silico modelling and simulation for dosage selection in pediatric patients including neonates.

S. Leroux, W. Zhao, **E. Jacqz-Aigrain**

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Summary

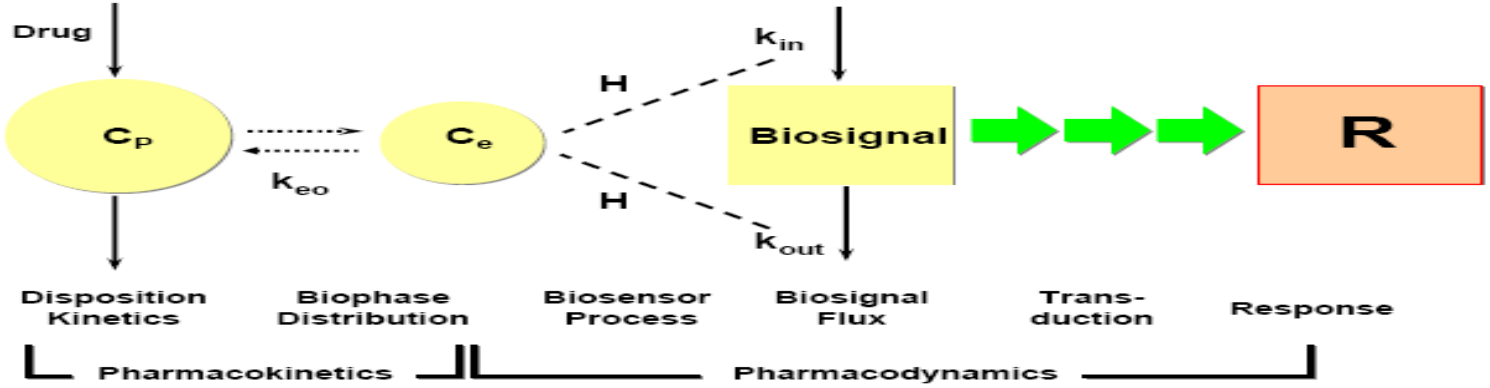
Population pharmacokinetics (Pop-PK), modelling and simulation were conducted to evaluate the pharmacokinetics and variability of currently used drugs in paediatric patients of different age groups (from neonates to adolescents) with different diseases.

- Ciprofloxacin in neonates and patients with sickle cell disease
  the corresponding studies are presented as an example in the following slides
- Vancomycin in neonates (*including a large meta-analysis within NeoVanc*)
  and patients with hemato-oncologic diseases
- Metronidazole in neonates
- Ceftazidime in patients with cystic fibrosis
- Ganciclovir
- Fluconazole
- Cyclosporine …

To recommand adapted drug dosage in children, based on innovative methods

Context

Complex modelling methods of population pharmacokinetics (Pop-PK), pharmacokinetic-pharmacodynamic (PKPD) or physiologically-based pharmacokinetic (PBPK) modelling are currently used, requiring analysis of covariates, that may participate to variability in drug disposition and responses.



Jusko et. al., JPB 23: 5, 1995

Objectives

To develop PK modelling and simulation methods to investigate the impact of key potential covariates on drug disposition of currently used drugs in pediatric patients

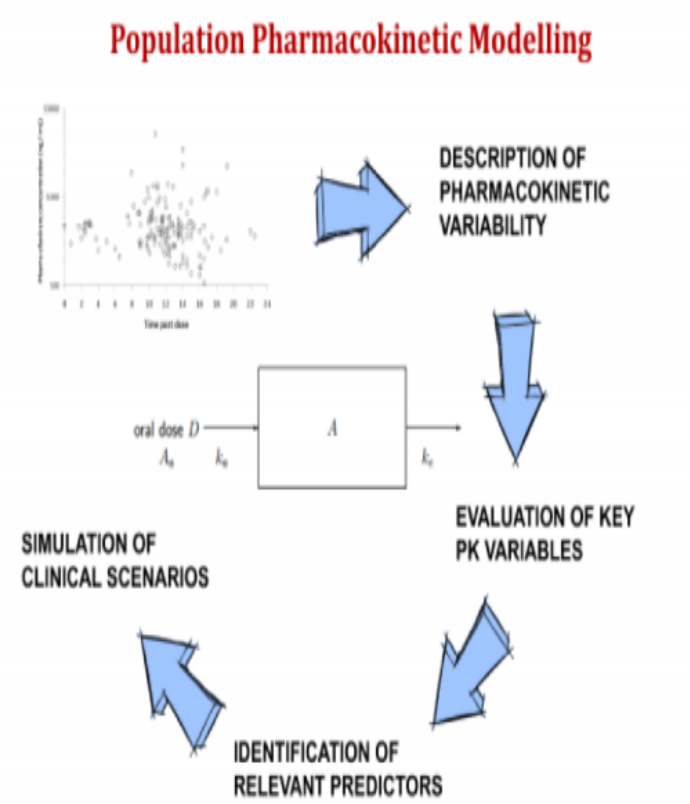
Age and age groups

from neonates to children

Different pediatric disease:

neonatal infection, sickle cell disease, cystic fibrosis, hemato-oncologic disease

Ethnicity



In silico modelling and simulation for dosage selection in pediatric patients including neonates

Ciprofloxacin in sickle cell disease

J Antimicrob Chemother
doi:10.1093/jac/dky328

Journal of Antimicrobial Chemotherapy

Variability of ciprofloxacin pharmacokinetics in children: impact on dose range in sickle cell patients

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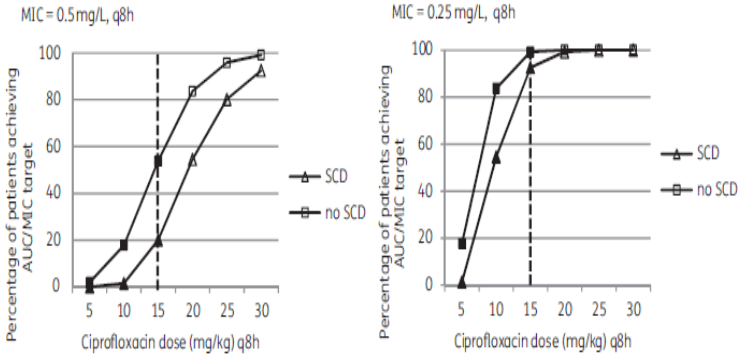
60 patients (4 months to 18.9 years) with SCD or other various diseases
Ciprofloxacin clearance : 0.77 ± 0.18 L/h/kg,
depends on : weight, creatinine concentration
Is 52% higher in SCD compared to non-SCD patients.
Monte-Carlo simulations show that the dose required to target the AUC/MIC over 125 required for antibacterial efficacy is higher in SCD

Modification of dosing regimens is recommended.

60 patients (0.3 - 18.9 years)
Ciprofloxacin clearance (0.8 + 0.3 L/h/kg)
depends on :
- WT and AGE
- Serum creatinine concentration



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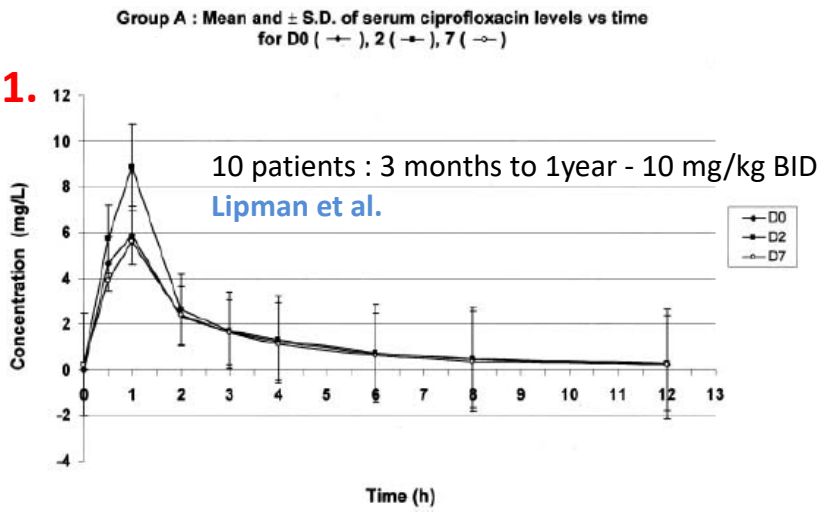
The exemple of ciprofloxacin :

1) Pharmacokinetics in neonates

1.



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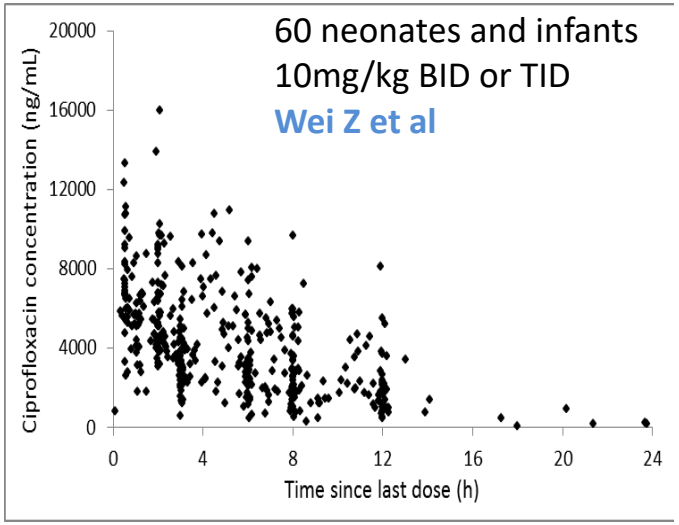
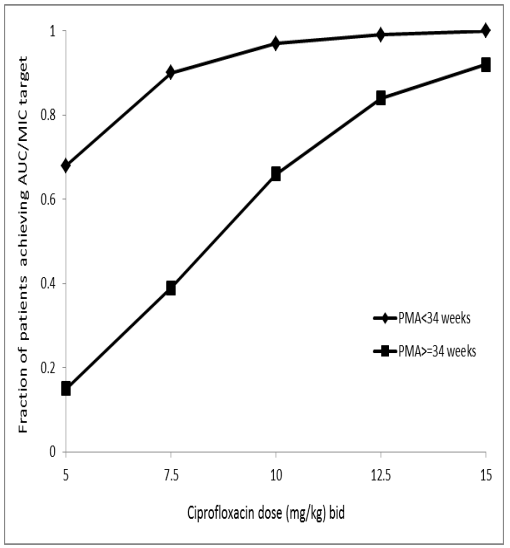


3.

Table 2 - Population pharmacokinetic final model parameters of ciprofloxacin and bootstrap results

Parameters	PK scavenged samples Estimate (RSE %)	Boostrap n=500 Median	Boostrap n=500 5th-95th CI	PK specific samples Estimate (RSE %)	Boostrap n=500 Median	Boostrap n=500 5th-95th CI
V1 (L)						
V1= θ1× (CW/1955)						
θ1	0.72 (36.0)	0.68	0.19 - 2.6	2.48 (9.2)	2.38	0.80 - 3.18
V2 (L)						
V2= θ2× (CW/1955)						
θ2	3.52 (9.2)	3.49	2.09 - 4.16	1.64 (14.5)	1.71	1.21 - 3.62
Q (L/h)						
Q= θ3× (CW/1955)$^{0.75}$						
θ3	3.32 (18.4)	3.14	0.63 - 4.52	1.33 (17.3)	1.37	0.41 - 6.14
Cl (L/h)						
CL= θ4 × (CW/1955)$^{0.75}$ × Fage × RF × $F_{inotrope}$						
θ4	0.334 (6.0)	0.334	0.30 - 0.39	0.355 (6.0)	0.356	0.31 - 0.40
FPNA=(GA/27.9)$^{\theta5}$×(PNA/27)$^{\theta6}$						
θ5	1.94 (14.4)	1.87	1.28 - 2.46	2.03 (11.4)	1.95	1.15 - 2.49
θ6	0.49 (27.5)	0.49	0.02 - 0.611	0.43 (13.0)	0.403	0.02 - 0.578
RF= EXP((CREA-42)× θ7)						
θ7	-0.007 (22)	-0.007	-0.011 - -0.003	-0.008 (22.0)	-0.009	-0.029 - -0.004
$F_{inotrope}$						
θ8	/	/	/	0.754 (11.6)	0.77	0.608 - 1.08
Inter-individual variability (%)						
V1	/	/	/	41.83 (21.0)	45.0	17.6 - 81.3
V2	/	/	/	72.18 (48.0)	72.2	24.3 - 169.6
CL	40 (24.4)	39.1	30.3 - 50.9	33.91 (21.0)	34.5	26.9 - 47.5
Inter-occasion variability (%)						
CL	/	/	/	/	/	/
Residual variability (%)	20.71 (24.0)	20.2	14.7 - 24.4	18.95 (29.8)	17.9	10.0-24.3



4.

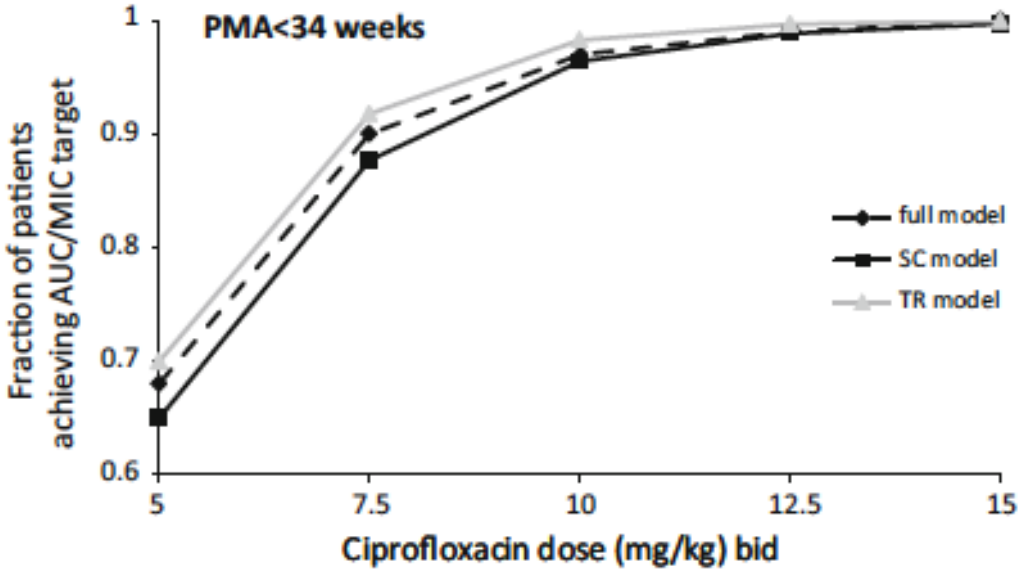
1) 90% of NN with PMA< 34 weeks 7.5 mg/kg BID
and
2) 84% of NN with PMA≥34 weeks receiving 12.5 mg/kg TID would reach the AUC/MIC target of 125

Clin Pharmacokinet
DOI 10.1007/s40262-015-0291-1

ORIGINAL RESEARCH ARTICLE

Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design

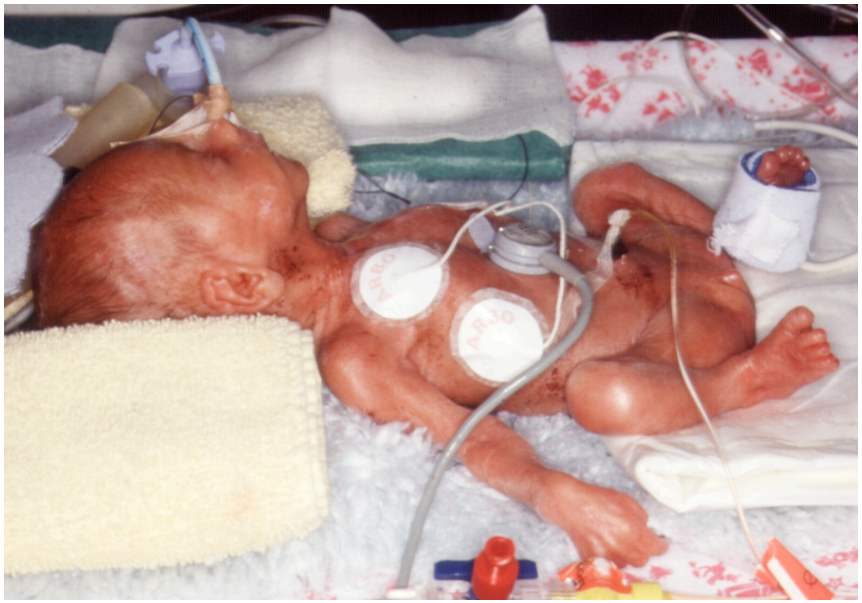
Stéphanie Leroux[1,2,3,4] · Mark A. Turner[5,6] · Chantal Barin-Le Guellec[7] · Helen Hill[5,6] · Johannes N. van den Anker[8,9,10,11] · Gregory L. Kearns[12,13] · Evelyne Jacqz-Aigrain[1,2,3,14] · Wei Zhao[1,2,3,14,15] · On behalf of the TINN (Treat Infections in NeoNates) and GRiP (Global Research in Paediatrics) Consortiums



An appropriately constructed population PK model using opportunistic samples can reliably estimate important PK parameters needed to support individualization of therapy in neonates

Vancomycin pharmacokinetic meta-analysis

Demographic characteristics of the 1631 neonates and infants included



Weight (CW)	415 g
GA	22.3 weeks
PMA	23.3 weeks
PNA	1 day
Birth weight	385 g

Median values	
Weight (CW)	1370 g
GA	30 weeks
PMA	32 weeks
PNA	11 days
Birth weight	1238 g
Creatinine	54 µmol/L

Weight (CW)	11.4 kg
GA	42.1 weeks
PMA	52.4 weeks
PNA	90 days
Birth weight	4.8 kg

Vancomycine dosage recommendation

target : daily AUC of 400 mg*h/L

PMA (weeks)	<29	29-35	>35	Total
Number of patients	335	618	510	1463
Standard dose regimen (mg/kg)	15 OD	15 BID	15 TID	
First day				
AUC_{0-24} median (mg*h/L)	246	378	495	385
AUC_{0-24} 5^{tn}-95^{tn} (mg*h/L)	163-356	264-523	332-725	203-638
Target attainment rate (%)	1.5	39.0	81.0	45.1
Steady-state				
AUC_{ss} median (mg*h/L)	337	535	651	519
AUCss 5^{tn}-95^{tn} (mg*h/L)	203-549	326-883	367-1291	260-1030
Target attainment rate (%)	28.0	83.9	91.8	73.9

PMA (weeks)	<29	29-35	>35
Reference dose (mg/kg)	15 OD	15 BID	15 TID
Simulated dose Loading dose Maintenance dose	25 15 BID	25 15 BID	25 15 TID

Conclusion

Pop-PK and PBPK modelling are of particular interest to explore drug disposition children, when data are limited and/or the impact of the disease usually unknown.

Information on drug / administration/ concentrations

In paediatrics, key covariates may include :

- Age (GA, PNA, PMA in neonates)
- Weight (birth weight, current weight) and BMI
- Biomarkers (renal / hepatic functions, pharmacogenetics…)
- Disease : hemato-oncology, cystic fibrosis, sickle cell disease
- Care and treatments : Co-administered drugs, ventilation, hydratation

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The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to EPTRI or the EC

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