POPULATION PHARMACOKINETIC OF LINEZOLID IN INPATIENTS

Thu Thuy Nguyen (1), Laurent Massias (2), Gilles Defrance (3), Nadège Bourgeois-Nicolaos (3,4), Xavier Duval (5), France Mentré (1), Antoine Andremont (6,7) and the LINEZOLIDE study group

(1) UMR738 INSERM - Université Paris Diderot, Paris, France; (2) Service de Pharmacie Clinique et des Biomatériaux, Hôpital Bichat, AP-HP, Paris, France; (3) EA4065 UFR des Sciences Pharmaceutiques et Biologiques - Université Paris Descartes, Paris, France; (4) Laboratoire de Bactériologie-Hygiène, Hôpital Béclère, AP-HP, Clamart, France; (5) CIC, Hôpital Bichat, AP-HP, Paris, France; (6) EA 3964 Université Paris Diderot, Paris, France; (7) Laboratoire de Bactériologie, Hôpital Bichat, AP-HP, Paris, France

BACKGROUND

- **Linezolid**
  - The first antibiotic of a new class of antimicrobial agents: the oxazolidinones
  - Approved for clinical use in United States in 2000 and in Europe in 2002
  - Against gram-positive bacteria
- **LINEZOLIDE trial**
  - Prospective, multicentric, observational trial in inpatients
  - Sponsor: French National Institute for Health and Medical Research (INSERM)
  - Objective: to study the impact of linezolid on human commensal flora in inpatients

⇒ **A pharmacokinetic (PK) sub-study was performed**

OBJECTIVES

To characterize the PK of linezolid in inpatients using a population approach

- Analysis of the plasma concentrations collected on day 7 (D7)
- Evaluation of the bioavailability of linezolid
- Evaluation of the effect of different covariates on the PK of linezolid

METHODS

- **Population study**
  - 28 inpatients
    - Treated by linezolid for the first time
    - Administration

      oral: 17 patients
      intravenous (IV) with infusion duration of 1 h: 8 patients
      relay oral/IV before D7: 2 patients
      relay oral/IV after D7: 1 patient

      } identical dose of 600 mg twice a day
- **Plasma linezolid concentration measurements**
  - Four blood samples collected on D7 at 0 h (before dosing), 1.5, 4 and 8 h (after dosing)
  - Concentrations assayed by high performance liquid chromatographic (HPLC) method

  (the sample before dosing corresponds to the trough concentration

  ⇒ *concentrations at 0 h considered in the modelling as the ones at 12h after dosing)*
- **Pharmacokinetic model**
  - Combining the two administration modes, written with MLXTRAN in MONOLIX 3.1 [1]
    - first order absorption for oral administration parameterized in absorption rate constant ka
    - volume of distribution V
    - first order elimination parameterized in clearance Cl
    - biodisponibility F
  - ka fixed to 2.7 h^{-1} [2]
- **Population analysis**
  - Modelling jointly data of all patients by nonlinear mixed effects model
    - Exponential model for the random effects
    - Diagonal variance-covariance matrix
    - Combined error model
  - Test whether F different from 1
  - Estimation of the population parameters & their variability by SAEM algorithm [3] in MONOLIX 3.1
- **Covariates**
  - Continous covariates (height, weight, age) centered by mean
  - Categorical covariate (sex): reference = woman
  - Missing data for covariates height & weight (in 10 & 3 patients respectively) replaced by the mean of the corresponding covariates
  - Univariate analyses by including one by one covariate in the basic PK model + Wald tests on the effect of each covariate on each PK parameter
  - Forward LRT selection of the covariate model for covariates having significant effect on PK parameters

RESULTS

- **Demographic characteristics of the 28 patients (15 women, 13 men) at enrollment**

Characteristic	Mean	SD	Median	Range
age (years)	62.7	18.5	63.2	26.5-85.8
height (cm)	171.0	12.7	171.5	150.0-195.0
weight (kg)	73.5	17.3	70.0	36.0-130.0

- **Observed concentrations and model predicted curves**

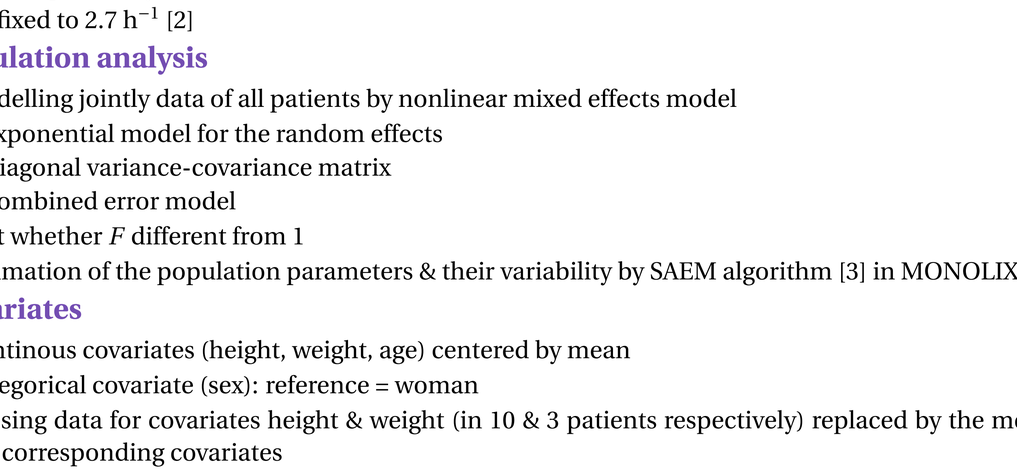

Fig 1: Individual concentrations of linezolid and model predicted curves (in colors) from estimated population parametres

- **Population pharmacokinetic of linezolid**
  - A one compartment model with first order linear elimination and with first order absorption for oral administration adequately describes concentrations for all patients

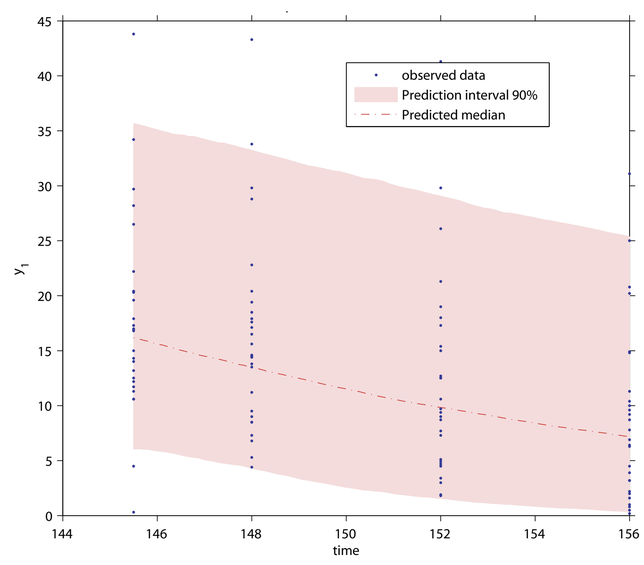

Fig 2: Visual predictive checks (VPC)

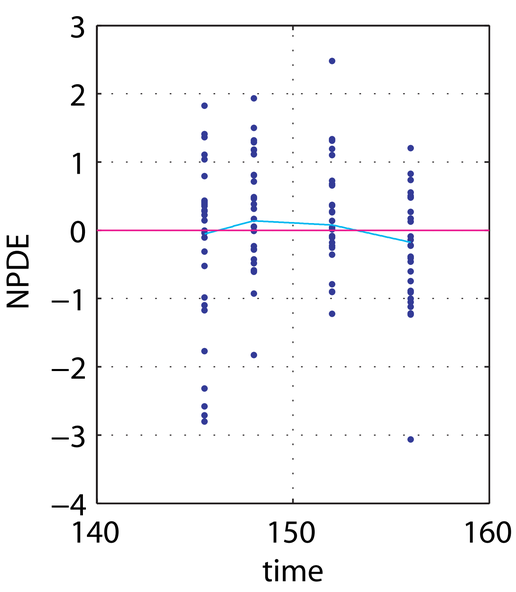

Fig 3: Normalized prediction distribution errors versus time

  - F not significantly different from 1
    - non significant LRT (p=0.31); non significant Wald test (p=0.88)
    - F estimated = 1.17 with standard error = 0.14; 95%CI of F = [0.89;1.44]

      ⇒ fixed to 1 in the chosen model
  - PK parameter estimation

		Basic model		**Covariate model**	
Parameter	Estimates	RSE (%)	Estimates	RSE (%)
k_a (h^{-1})	2.7	–	2.7	–
V (L)	47.5	8	47.1	8
Cl $(L.h^{-1})$	4.37	12	4.31	9
$\beta_{Cl,weight}$	–	–	1.33	31
$\beta_{Cl,age}$	–	–	-0.81	33
ω_{ka}	1.92	28	2.67	22
ω_V	0.242	39	0.243	40
ω_{Cl}	0.611	14	0.445	14
$a(ng/mL)$	1.16	26	1.15	26
b	0.07	37	0.07	37

- **Effect of covariates**
  - Significant effects of weight (p=0.0013) and age (p=0.0026) on Cl

    When weight increases of 10 kg from the mean weight, Cl increases of 18.6%

    When age increases of 10 years from the mean age, Cl decreases of 11.1%
  - No effect of height and sex on PK parameters

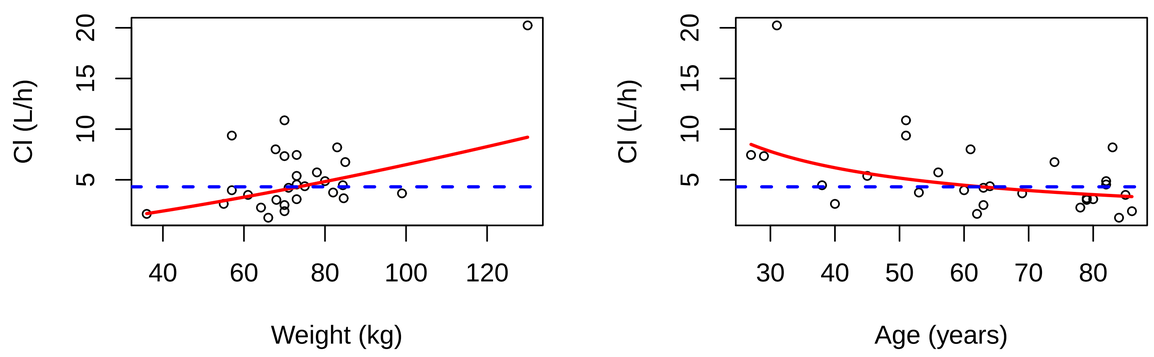

Fig 4: Individual values of clearance parameter in function of inpatient weight and age

(the blue dotted line represents the population parameter Cl; the red curve represents the model explaining Cl in function of weight or age)

CONCLUSION

- The population PK of linezolid described by a one compartment model combining oral and IV administrations using MLXTRAN in MONOLIX 3.1
- Confirmation of the 100% bioavailability of linezolid [4]
- Effect of inpatient weight and age on linezolid clearance

[1] www.monolix.org

[2] McGee, B., Dietze, R., Hadad, D.J., Molino, L. P., Maciel, E. L., Boom, W. H., Palaci, M., Johnson, J. L., Peloquin, C. A. Population pharmacokinetics of linezolid in adults with pulmonary tuberculosis, *Antimicrobial Agents Chemotherapy* 2009, 53:3981-3984.

[3] Kuhn, E., Lavielle, M. Maximum likelihood estimation in nonlinear mixed effects model, *Computational Statistics and Data Analysis* 2005, 49:1020-1038.

[4] Welshman, I.R., Sisson, T.A., Jungbluth, G.L., Stalker, D.J., Hopkins, N.K. Linezolid absolute bioavailability and the effect of food on oral bioavailability. *Biopharmaceutics and Drug Disposition* 2001, 22:91-97.