The Use of Indirect Response Model to Assess Interaction Between Drugs: acenocoumarol and amoxicillin + clavulanic acid

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Introduction

- Acenocoumarol is an oral anticoagulant frequently prescribed with antibiotic association amoxicillin plus clavulanic acid (AM+AC)
- Literature data: 7 cases reports and 1 case control trial reporting an increase in anticoagulation level
- Aim of this study: to investigate the influence of AM+AC on PK-PD of acenocoumarol

Description of the study population

Variables	Mean	SD	Min	Max
Age (yrs)	23.9	3.3	20.0	29.0
Weight (kg)	68.1	8.9	60.0	85.0
Height (cm)	175.9	7.2	164.	186.0
BSA (Kg/m²)	1.822	0.1	1.7	2.1
BMI (m²)	22.03	2.6	18.5	26.2
TPr T0 (%)	88.1	11.2	72.0	100.0

Trials included in the meta-analysis

# Study	Population		Samples / subject	Dose
Study #1 (current trial)	8 healthy volunteers	8 males Age: 24 ± 3 WGT: 68 ± 9	11	8 mg at day 1
Study #2 [1]	23 healthy volunteers	20 males Age: 27 ± 8 WGT: 70 ± 10	8	4 mg at days 1,2
Study #3 [2]	8 healthy volunteers	8 males Age: 25 ± 2 WGT: 72 ± 9	11	12 mg at day 1

PK results

- 2 compartment model with first-order absorption and lag-time
- inter-individual variability on CL,V2,V3, Ka, Lag
- covariates: Weight on V2 and AM+AC on Cl

Methods

Design

- 8 healthy volunteers
- Single dose of 8 mg of acenocoumarol on day 1 and 8
- 1g of amoxicillin + 250 mg of clavulanic acid from day 3 to 9

Blood samples and dosage

- 11 blood samples at day 1 and at day 8.
- Acenocoumarol PK dosage: HPLC, Lichrosorb SRP 18 Chrompack
- Acenocoumarol PD marker: prothrombin time ratio (PTr), chronometric method, Diagnostica Stago

PK/PD analysis

- 1st step: structural identification of PK model by meta-analysis
- 2nd step: an indirect PK/PD model was build conditional on the individual bayesian PK parameters estimations

$$\frac{dCF}{dt} = kin \times \left[1 - \frac{Cp^{\gamma}}{Cp^{\gamma} + C_{50}^{\gamma}}\right] - kout \times CF \quad [3] \qquad PTr = PTr0 \times \frac{CF}{(\theta + CF)}$$

CF=clotting factors; Cp=Plasmatic concentration; PTr=prothrombin time ratio

- Covariates: volunteers characteristics, co-administration of AM+AC
- NLME model in NONMEM V (FOCE INTERACTION)

Model validations

- Comparison between observed (DV) and prediction (PRED) of the model (Xpose 4 [4])
- Visual predictive Check: simulation of 500 new datasets using point estimates of final parameters (PsN script [5])

PD results

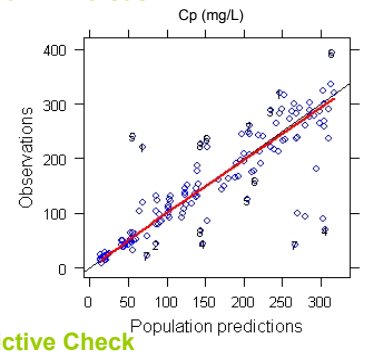
- The final model included 4 parameters with 2 hyperbolic functions: SYNTH, C50, E0, θ_H
- Hill coefficient over parameterized the model
- No covariate directly influenced PTr

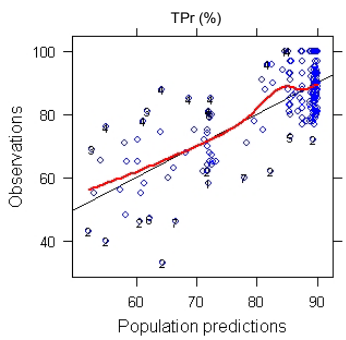
PK and PD parameter estimates

Parameters	Pop value	Inter-individual variability (%)
CL (L/h)	4.08	5.09
TTT on CL	0.875	
V2 (L)	24.5	2.07
WGT on V2	1.03	
Q(L/h)	1.8	0 fix
V3 (L)	11.8	0.5
Ka (h⁻¹)	4.04	79
Alag (h)	0.404	14.5
Residual error on PK (%)	23.8	
Kin (h⁻¹)	0.175	0.86
C50 (mg/l)	1.69	52.2
PTr0 (%)	94.4	6.47
θ_H	0.0510	0 fix
Additive residual error on PD (%)	27.8	

Validation

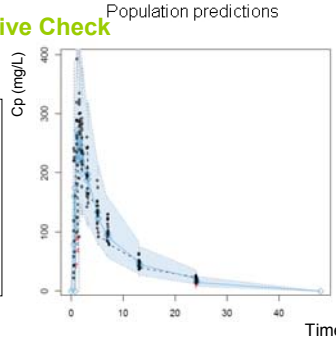
Comparison of DV versus PRED

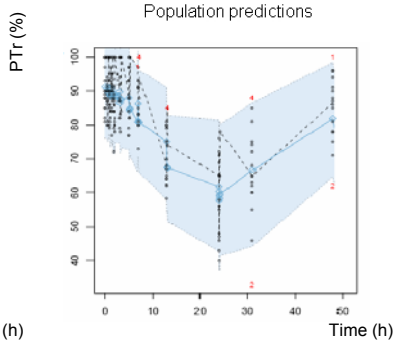




Visual Predictive Check

- blue envelope: 95% prediction interval
- red numbers: observations out the prediction interval





Discussion

- An indirect response model applied to PK-PD data of acenocoumarol
- To our knowledge: first application of an indirect response model to detect drug-drug interaction
- AM+AC interaction on acenocoumarol PK level ➔ 12.5% decrease in CL but no explicit pharmacological mechanism
- AM+AC do not seem to affect acenocoumarol PD assessed by PTr
- Limits of study : no cross-over, maximum effect for 8 mg of acenocoumarol

References

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