Prediction of power of test of discrete covariates in population analyses and influence of design: application to gender effect in joint pharmacokinetic models of nucleoside analogs and their active metabolites

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Context

Population design evaluation and optimization for multiple response models[1]

- Methodology based on the Fisher information matrix (M_F)
- Linearization of M_F using a first order Taylor expansion

Extension of this methodology for models with parameters quantifying influence of discrete covariates[2,3]

- Prediction of the power of the Wald test of a discrete covariate
- Computation of the number of subjects needed to achieve a given power

➔ Implementation in PFIM (a R function)

Nucleoside reverse transcriptase inhibitors (NRTI)

- Antiretroviral therapy for HIV infected patients
- Metabolism of NRTI in an intracellular triphosphate (TP) metabolite
  - Active metabolite: important for efficacy and toxicity of NRTI
  - Complex and costly assay for measurement of intracellular concentrations

Clinical trials on pharmacokinetic (PK) of NRTI[4,5]

- Clinically important gender differences on intracellular concentrations

Cophar 2 ANRS111 trial[6]

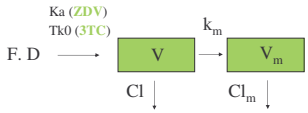
- PK of 2 NRTI: Zidovudine (ZDV) and lamivudine (3TC)

Objectives

To predict power of tests of gender effect and to study the influence of design in population pharmacokinetic analyses of nucleoside reverse transcriptase inhibitors and their active metabolite

Population pharmacokinetic analyses of NRTI and intracellular metabolite

Pharmacokinetic models[7]



- Identifiable parameters: ka, Cl/F, V/F, Clm/(Fkm), Vm/(Fkm)

Population design (*empirical design*)

- Plasma concentration of ZDV and 3TC at steady state
  - 75 patients with 4 samples before and at 1, 3 and 6h after drug administration
- Intracellular concentrations of ZDV-TP and 3TC-TP at steady state
  - 62 patients
    - 11 patients with 4 samples before and at 1, 3 and 6h after drug administration
    - 26 patients with 2 samples at 3 and 12h after drug administration
    - 25 patients with 1 sample at 3h after drug administration

Population analysis

- Exponential model for the random effects
- Additive and proportional error model
- SAEM algorithm implemented in the Monolix V2.3 software

Inclusion of a gender effect *β* on the apparent metabolite clearance

- 62% of Female / 38% of Male
- ZDV-TP: Clm/(Fkm) increase of 30% in male (Wald test: p = 0.16)
- 3TC-TP: Clm/(Fkm) decrease of 2.8% in male (Wald test: p = 0.46)

Table1. Population parameter estimates (inter-subjects variabilities in %).

	Ka / Tk0	Cl / F	V / F	$Cl_m/(Fk_m)$	$V_m/(Fk_m)$	β [95% CI]
ZDV	2.86 h^{-1} (-)	200 $L.h^{-1}$ (54%)	234 L (77%)	175 L (58%)	2.71 10^3 $L.h^{-1}$ (-)	0.287 [0.115; 0.688]
3TC	1.24 h (74%)	22.1 $L.h^{-1}$ (31%)	94.8 L (24%)	0.91 L (47.5%)	28.0 $L.h^{-1}$ (-)	-0.028 [-0.288;0.232]

Prediction of the power to detect gender effect

Study only for ZDV *(Very small gender effect on 3TC)*

- Using the parameter estimates presented in Table1
  - Evaluation of the empirical design with PFIM 3.2
    - Computation from the predicted SE of β on Clm/(Fkm) with PFIM
      - Expected power to detect gender effect
      - Number of subjects needed for a power of 80%
      - Type I error equal to 0.05

➔ Expected power to detect gender effect: 31%

➔ Number of subjects needed to detect gender effect for a power of 80%: 273 subjects

Figure1. PFIM 3.2 output for computation of the expected power and the number of subjects needed for a power of 80% to detect a gender effect on Clm/(Fkm).

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****************************** EXPECTED POWER ******************************

With a Type I error equal to 0.05 :

                    Beta      95% CI Expected_power
beta_Clm_Gender_2 0.287 [-0.1;0.67]       0.3051932


********************* NUMBER OF SUBJECTS NEEDED ************************

With a Type I error equal to 0.05  and with a given power equal to 0.8 :

                    Beta      95% CI   exp(Beta)     95% CI  Number_subjects_needed
beta_Clm_Gender_2 0.287 [-0.1;0.67]    1.332424 [0.9;1.96]          272.3515
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Design / power optimisation

Optimization with PFIM[8]

- D-optimality: det(M_F)
- Federov-Wynn algorithm (FW)
  - Optimization of the number of subjects
  - Optimization of the sampling times in a given set specified by users
    - → For a total cost of 400 samples as in the empirical design
- Optimal " identical" design
  - 4 identical sampling times for ZDV and ZDV-TP
  - 12 allowed sampling times among 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12h
- Optimal "different" design
  - $t_{1/2}$ different for ZDT and ZDV-TP → Different sampling times
  - 1, 2, 3 or 4 sampling times per patient
  - Allowed sampling times: only ≤ 4h for ZDV

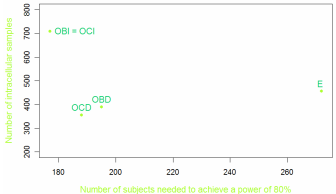
Table2. Design optimized using models without or with covariate.

	Basic model (with no covariate)	Covariate model (with gender effect)
"Identical" design	Opt_Basic_Iden	Opt_Cov_Iden
"Different" design	Opt_Basic_Diff	Opt_Cov_Diff

Table3. Influence of the design on the number of subjects needed to achieve a power of 80% including parameters influencing by discrete covariates.

Design	Sampling times ZDV	Sampling times ZDV-TP	Proportions of subjects (%)	Number of subjects needed	Number of plasma samples	Number of intracellular samples	Total number of samples
Empirical (E)	1, 3, 6, 12	-	15	273	1092	456	1548
	1, 3, 6, 12	1, 3, 6, 12	15				
	1, 3, 6, 12	3,12	37				
	1, 3, 6, 12	3	33				
Opt_Basic_Iden (OBI)	0.5,1, 3, 12	0.5,1,3,12	1	177	708	708	1416
Opt Cov_Iden (OCI)	0.5,1, 3, 12	0.5,1,3,12	1	177	708	708	1416
Opt_Basic_Diff (OBD)	0.5,1, 3	3,12	1	195	585	390	975
Opt_Cov_Diff (OCD)	0.5,1, 3	2, 12	74	188	535	356	891
	0.5, 2	2,12	15				
	0.5, 1, 3	12	11				

Figure2. For the different designs, number of subjects needed and intracellular samples.



- For a power of 80%
  - Optimal designs vs empirical design
    - → Less patients
    - → Less intracellular measurements
  - Optimal "different" designs vs optimal "identical" designs
    - → Less intracellular measurements

=> More reasonable cost

Conclusion

- Illustration of the influence of the design and the number of subjects needed to achieve a given power of the Wald test of discrete covariate for complex PK models
- Great potential of PFIM 3.2 to optimize design and to control expected power of a Wald test
- Extension of this work to compute power of test of absence of covariates → bioequivalence tests

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